Part I Introduction
Introduction

Pediculosis capitis is a very common infestation, mainly affecting children between 3 and 12. However, adolescents and adults can also be infested. The prevalence of head lice differs from country to country and depends on the diagnostic criteria and methods used. Nevertheless, in school children in industrialised countries active infestation rates around 10% are frequently reported\(^{1-4}\) and higher prevalences are not exceptional.\(^5,6\)

Even though head lice infestations cause clinical lesions and physical discomfort, their medical importance derives from their psychological, financial and social impact. Head lice cause social distress at school and in the family\(^7\) and are associated with feelings of shame and disgust.\(^8\)

The direct costs for pediculicides and louse combs associated with pediculosis are impressive. Estimates for the costs of pediculicides in the USA (total population of almost 300 million) are between $240 million\(^9\) and $367 million.\(^10\) In Belgium (total population just over 10 million) over €4 million was spent on pediculicides in 2002.\(^11\)

Indirect costs associated with pediculosis are difficult to estimate. In schools with a “no-nit policy” children are sent home for as long as nits are present in the hair. These children must be cared for by a parent leading to absence from work and loss of parental wages.\(^10\) This policy obviously has an important impact on the child’s education.\(^9\)

Pediculosis has a large financial and social impact on the child, its family and the community which indicates that this problem needs a specific and well designed management.

Scabies is not a life threatening condition but nevertheless it is a nuisance for the affected individual because of the rash and the intense and persistent pruritus that can be depressing and severely debilitating.\(^12\) However, scabies has a large impact on public health. It is estimated that 300 million new cases of scabies occur worldwide every year.\(^13\) Scabies is endemic in many resource poor communities. In developed countries on the other hand, institutions and social disadvantaged populations are particularly at risk of large outbreaks. The costs that are involved with
the management of scabies in institutions are considerable. An early diagnosis, efficient therapy and identification of persons or groups at risk are of paramount importance in the management of scabies.

Pediculosis and scabies are closely related skin conditions. Both are caused by ectoparasites, transmission usually occurs through close contact with infested persons and itch is a typical clinical sign. Furthermore, some chemical compounds, such as permethrin, are used in the treatment of both diseases.

The management of pediculosis and scabies should incorporate an accurate and early diagnosis, identification of persons or groups at risk, effective treatment and appropriate preventive measures. For the development of a qualitative management for both diseases, the principles of evidence-based medicine can be used as guidance.

Evidence-based medicine (EBM) is a relatively new way of practicing and teaching medicine which has gained considerable respect over the last 15 years. Until about 40 years ago it was assumed that every physician thought and handled in the correct way. Knowledge was gathered from the unsystematic observations of clinical practice and insight into the patho-physiology and mechanisms of disease was regarded as the only guide for clinical practice. Traditional medical observation and common sense were regarded as sufficient to provide the background and skill necessary to evaluate new tests and treatments. Guidelines for practice were usually based on expert opinion or a consensus of experts. A classic medical education followed by continuing education obtained from journals, individual experiences and contacts with colleagues were considered the way to acquire knowledge. However, in the seventies and eighties it became apparent that physicians could not process all the information necessary for a complex medical decision on this basis, and that decision should not be based on the art of medicine or clinical judgement alone. Several publications demonstrated that there was a wide variation in practice patterns and that different physicians applied different practices to essentially the same type of patients. Furthermore, there was a wide gap between clinical research and clinical practice. There was a lack of good evidence for some medical practices and moreover many practices were found ineffective in clinical trials. It was
in this context that a shift occurred from the paradigm of classic medicine to the new concept of evidence-based medicine.\textsuperscript{16}

EBM was first described in a paper produced by the EBM working group in 1992 and it was defined and discussed in a frequently cited paper by Sackett et al. in 1996.\textsuperscript{16,18}

In a recent definition EBM is described as "... the integration of the best research evidence with our clinical expertise and our patients unique values and circumstances." Clinical expertise is the ability to use clinical skills and past experience to make a more effective and efficient diagnose. It enables us to identify each patient's personal circumstances and expectations. Patient values stands for the unique preferences, concerns and expectations of each patient which must be integrated into clinical decisions. The patient’s circumstances are the individual clinical state and setting.\textsuperscript{19} The best available research evidence is defined as valid and clinically relevant patient-centred research. Systematic reviews, meta-analyses of randomised controlled trials (RCT) and RCT’s are regarded as the highest level of evidence.

The availability of evidence (or rather the lack of it) has been identified as one of the problems in the practise of EBM and is particularly problematic in the area of pediculosis and scabies because little evidence has been generated in these fields. Recently attention has also been drawn on the fact that, apart from medical evidence, there is also a need for contextual and policy evidence. Contextual evidence deals with the challenge of treating a particular patient in a specific situation. For instance, what treatment can be prescribed if the standard treatment is too expensive for your patient? Policy evidence addresses the optimal allocation of resources.\textsuperscript{20}

As a first step towards the development of an evidence-based management of pediculosis and scabies, we outlined research questions that are crucial for rational therapy of head lice and scabies. The research questions are summarised in the overview on page 5.

In this thesis we attempted to find an answer for the research questions by systematically collecting all available evidence and by providing new evidence through original research.
Part II: Pediculosis

Diagnosis:
- What is the accuracy of the methods for detection of pediculosis described in the scientific literature?
- What are the costs of these detection methods?
- What is the place of these detection methods in the screening for pediculosis?

Epidemiology
- What is the prevalence of pediculosis in schoolchildren between 3 and 12 years of age in Belgium?
- What are the risk factors for pediculosis in this population?

Treatment
- What are the treatment options for pediculosis, what is their value and place and what evidence is there to support their use?
- Which products are efficacious for the removal of the eggshells from human hair?

Management
- Who should be involved in the management of pediculosis, what is the role of each partner and how can a strategy be implemented?

Part II: Scabies

Diagnosis:
- What are the key elements for the diagnosis of scabies and what is the value of diagnostic techniques?

Epidemiology
- What is the incidence of scabies in Belgium?
- What are the risk factors for scabies in Belgian patients?

Treatment
- What are the treatment options for scabies, what is their value and place and what evidence is there to support their use?

Management
- Is there a deficit in the knowledge about scabies among GP’s and dermatologists in Belgium?
- What steps are important when handling a case of scabies?

Overview of research questions in this thesis.
Part II Pediculosis
1. Introduction

Pediculosis capitis is caused by *Pediculus humanis capitis*, the human head louse. *P. humanus capitis* belongs to the Anoplora or sucking lice together with *P. humanis corporis* or the body louse and *Phthirus pubis* or pubic louse. Head lice and body lice mainly differ in their habitat. Head lice are usually found on the scalp while body lice have their habitat in clothing and are only found on the body when feeding. Body lice presumably originated from head lice about 72000 years ago. Recent molecular research suggests that head lice and body lice do not interbreed and are probably separate species (in which case they should actually be named *P. capitis* and *P. corporis*). *Phthirus pubis* on the other hand belongs to another genus and is very different from the pediculidae.

The head louse is a dorsoventrally flattened insect with six legs. The legs end in a claw which is specially adapted to grasp a hair. Lice have no wings and cannot fly or jump. Adult lice crawl at a speed of approximately 12 cm/min. Younger stages are slower with first instars crawling at a speed of 6 cm/min. Lice are host specific, meaning that human lice can only live and reproduce on humans. Adult lice are about 3 mm long; males are slightly smaller than females. Males can also be distinguished from females by the presence of dark transverse bands on the dorsum of the abdomen. Furthermore their abdomen is rounded while the female abdomen terminates in two large posterior lobes, giving it a bilobed appearance (Fig. 1).

The life cycle of the head louse starts when the gravid female lays her eggs. The eggs are oval shaped, shiny and tan to brown coloured. The difference between empty eggshells (or nits), viable eggs and dead eggs will be discussed in Chapter 4 together with the way nits are attached to the hair and how they can be removed. In vitro studies have shown that a female louse lays an average of 6 eggs a day and a total of about 55 fertile eggs after a single insemination (during her fertile life).
The eggs hatch after seven to ten days and need the humid and warm climate of their host for a successful incubation. Temperatures between 24 and 37 °C with an optimum between 29 and 32°C are required for the eggs to hatch.24, 28 The nymphs moult 3 times over a period of another 7 to 10 days before the adult stage is reached.24 A hatched head louse lives for 23 to 30 days.29, 30 The survival of head lice away from the host is limited. They die of starvation after 55 hours at 23°C.24 They survive longer in colder than in warmer temperatures.21

There is a lot of controversy in the scientific literature on the transmission of head lice. It is generally agreed on that head-to-head contact is a definite mode of transmission but there is no consensus on the intensity or frequency of the contact needed for transmission. Opinions also differ on the importance of the transmission via inanimate objects, so called “fomites”.8, 31, 32

The spatial and kinetic patterns needed for transmission of lice from one hair to another were studied in vitro. Apparently lice do not transfer if a hair passes at an angle of 90° but only when it passes parallel to the hair on which they are clinging. There is almost no transfer on hairs passing dorsally or ventrally, most lice transfer on hairs passing lateral and preferentially from tail-to-head and at a slow speed. In only 7.1% of the attempts there was a transfer. These experiments suggest that repeated and prolonged head-to-head contact is required which is however not confirmed by real life experience.33
In vitro studies have shown that all stages are able to leave the host but adults stages have a greater tendency to look for a new host than nymphs. The authors conclude that adults are most likely responsible for initiating new infestations and they suggest that control measures should focus on this stage. Head lice are dislodged by using a hair dryer, a normal comb, towelling and friction of fabric. They can be removed with a vacuum cleaner but not with a dust buster (a small hand-held vacuum cleaner). Almost 60% of the eggs removed from the host hatch in 15 days if they are exposed to a human host for only 8 hours a day and kept at room temperature for the rest of the day. With this experiment the authors wanted to simulate a situation where eggs were removed from the host and left in the bed. These in vitro experiments illustrate that lice can actively leave the host or can be dislodged by manipulating the hair. However, several factors should be taken into account before this evidence is applied back to daily practice. First the risk of transmitting lice in a passive way depends on the number of lice per patient and the number of lice that are effectively dislodged. Transmission via fomites will obviously be more important in heavily infested cases than in mild cases. The risk of a new infestation after contact with fomites will also depend on the period during which the lice are away from a host. The longer they are deprived of a host, the lower the survival rate and the capacity to infest a new host. Transmission of lice through fomites is possible but it is probably less important in practice than head-to-head transmission.

Speare et al. investigated the role of bedding in the transmission of head lice. Two lice were found on 2 pillowcases out of 48. The subjects who used these pillowcases had 17 and 41 lice on their heads respectively. Lice are killed during a hot wash (66°C) or a cycle in a dryer (15 min at 70°C). Lice are not killed in a cold wash or by drying outdoors. The authors conclude that the transfer of lice to pillowcases occurs, but the incidence is low, and the number of lice per pillow case is also low. Similar results were found in a recent study by Izri and Chosidow. Lice and nits were killed by washing linen at a temperature of at least 50°C or a cycle in a dryer. Head lice experimentally placed on brushes and combs are killed after exposure for 30 seconds to water of 60°C.
Lice exclusively feed on the blood of their host. Fine stylets cut the skin and are inserted into a scalp capillary. The amount of blood lost in this way is less than 1 ml per month and will not result in anemia.\(^{39}\) When feeding, lice inject saliva into the host to promote vasodilatation. Saliva and fecal material provoke an immunologic response in the host which leads to the development of symptoms.\(^{40}\) The response to a bite changes in function of the duration of an infestation. In the first phase there are no clinical symptoms after a bite. In a second phase a papular reaction develops 24 hrs after the initial bite, together with moderate pruritus. In the third phase there is weal formation within 30 minutes and an intensive pruritus. In the fourth phase the reaction is attenuated with less pruritus and only a papular reaction.

Pruritus, excorations and bite reactions are the most common findings related to an active infestation.\(^{41}\) In severe cases there might be an associated pyoderma.\(^{42}\) However, little more than half of the infested children have clinical manifestations. Because pediculosis can occur without pruritus or other symptoms all members of a family have to be checked if one family member has head lice.

The estimates of the number of lice per patient differ. One study mentions an average of 30 lice per patient\(^ {39}\) while three quarters of the examined children had between 1 and 10 lice in another study.\(^ {4}\) The number of lice found per child depends highly on the method used to find them. Accurate studies on large series have not been done until now.

Head lice and body lice play a different role in public health. Body lice are known vectors of *Rickettsia prowazekii*, *Bartonella quintana* and *Borrelia recurrentis*. These pathogens are responsible for respectively louse borne epidemic typhus, trench fever and louse borne relapsing fever.\(^ {43,44,45}\) In general head lice do not transmit these pathogens. Studies however have demonstrated that head lice are capable of transmitting *Rickettsia* in vitro but the clinical importance is limited.\(^ {45}\) However it has been shown that they are able to spread *S. aureus* and *S. pyogenes*.\(^ {29}\) Until now, there have been no reports of head lice transmitting other infectious diseases.
Diagnosis, epidemiology, treatment, and general management of pediculosis will be discussed in detail in chapters 2, 3, 4 and 5, starting from the research questions listed in the general introduction.

The literature that is used to discuss the topics, was searched in a systematic way in order to find all relevant publications. Different databases were searched, such as PubMed and ISI Web of Science, using MeSH headings such as “Pediculus”, “Lice Infestations” combined with other headings and subheadings such as “Permethrin”, “diagnosis”, “therapy”, “transmission”,… This search was repeated regularly. Interesting literature, e.g. a PhD dissertation, was also found in references of some publications.
2. Diagnosis of pediculosis

Diagnostic techniques are a crucial element in epidemiological research and clinical trials. An accurate diagnosis is also the cornerstone of the management of infectious diseases. Undetected cases of pediculosis can act as a source of (re)infestation and hamper the effective management, even if detected cases are treated correctly. False positive diagnoses on the other hand will lead to unnecessary treatment. Furthermore, if a patient is evaluated post treatment and a false positive diagnosis is made, one could wrongly conclude that the treatment has failed. Therefore false positive diagnoses can also be a potential reason for “treatment failure”.

The diagnosis of pediculosis is based on two key elements: the diagnostic criteria and the diagnostic method.

The only correct definition of an active infestation is the presence of a living, moving louse and/or viable eggs. The presence of eggshells (either empty or containing a dead egg) is a sign of a past infestation and thus the latter obviously should not be used to diagnose active pediculosis.

Several methods have been described to diagnose an infestation. The oldest, traditional method is visual inspection (VI). The hair is parted with the fingers or applicator sticks and the scalp is inspected. Another method is dry combing (DC). First the hair is untangled using an ordinary comb. Then the hair is combed section per section using a fine toothed comb. An ordinary shampoo or a pediculicide is sometimes used to facilitate the detection of head lice. In “shampooing and straining” the hair is washed with an ordinary shampoo and the rinse water is collected and strained through a towel. Hair can be shampooed with a pediculicide before combing it with a fine toothed comb.

Finally, wet combing (WC) is a detection method in which water, conditioner and a fine toothed comb are used. First the hair is thoroughly wetted and ample conditioner is applied to the hair. The scalp is systematically combed lock by lock using the fine toothed comb while gently touching the scalp. After every stroke the comb is wiped on a tissue and checked for lice. The hair is rinsed when the entire scalp surface is
Part II: Pediculosis | Chapter 2 Diagnosis

combed. Then the procedure is repeated but this time the hair is combed from the nape of the neck towards the forehead. This method was derived from Bug Busting wet combing in which the hair is shampooed before applying the conditioner.\textsuperscript{47,51} The methods described above are used in epidemiological research and therapeutic trials.\textsuperscript{1,6,52-55} However, there are only two studies comparing the diagnostic performance of three, frequently used, detection methods. DC was found to be four times more effective than VI.\textsuperscript{49} In a comparison of VI with WC, VI resulted in 10% false negatives and 30% false positives.\textsuperscript{56} Until now, no gold standard for the diagnosis of pediculosis has been described.\textsuperscript{47}

From the available literature it seems that DC and WC are more accurate than VI. One could also suspect that WC might be more accurate than DC. In the first method, moist and conditioner are used to immobilise lice and this should facilitate detection. WC on the other hand implies more costs and is more time consuming.

In the current context, three important questions are identified:

- What is the accuracy of VI, DC and WC for detection of pediculosis?
- What are the costs of these detection methods?
- What is the place of these detection methods in the screening for pediculosis?

In an attempt to provide new evidence, we conducted original research which is summarised below.

In 2005 we screened 608 children between 2 and 14 years of age attending 4 primary schools and kindergartens in Ghent, Belgium. All children were consecutively screened on the same day with VI, DC and WC by 3 different, blinded screening teams.

The time needed to complete a detection method was registered using a stopwatch. Time started running as soon as detection was initiated and ended when the first living, moving louse was found or when the procedure was completed in the absence of lice. The cost to screen a child was estimated per method. The estimation was based on the cost for material that is strictly needed to perform the screening. Costs for tap water, material needed for administration or the laundering of towels were not
included. The cost for personnel was not included because large scale screenings are usually performed by a variable number of professionals, assisted by many volunteers.

This study was approved by the ethics committee of the University Hospital Ghent (2004/409) and all parents were asked for their consent.

All positive results were double-checked by an expert to avoid false positive diagnoses. Since all positive test results were confirmed cases of pediculosis, the specificity of each method used in this study was by definition 100%. Moreover, the sensitivity of each method can be expressed as the ratio of the prevalence of lice as detected by that method (numerator) and the true prevalence (denominator). Hence, under these particular circumstances, comparing sensitivities of screening methods is equivalent to comparing their detection rates. The McNemar test was used to compare related samples; the Kruskal-Wallis test was used to compare independent samples. The threshold for statistical significance was chosen at $\alpha=0.05$.

Head lice were found in 7.6 %, 15.0% and 18.8% of the children with respectively VI, DC and WC (Fig. 2). Nits in the absence of lice were found in 17.9 %, 9% and 8.1% with respectively VI, DC and WC.

The sensitivity of WC was 1.25 ($P = 0.002; \chi^2 = 9.49$) higher than of DC and 2.47 ($P < 0.001; \chi^2 = 59.07$) times higher than of VI. The sensitivity of DC was 1.98 times ($P < 0.001; \chi^2 = 33.97$) the sensitivity of VI. The costs per screened child were 57% higher with WC than with DC and the costs per detected case were 26% higher with WC compared to DC.
The median time to screen a child without head lice using VI, DC and WC was respectively 2'46", 3'10" and 5'31" (P < 0.001, Kruskal-Wallis test $\chi^2 = 325.62$, df 2). The median time needed to detect head lice with VI, DC and WC was respectively 2'54", 2'02" and 3'34" (P< 0.001, Kruskal-Wallis test = 42.33, df 2).

It seems that WC has a higher diagnostic performance than DC and VI but more expenses and human resources are needed. If the necessary resources are available, WC should be advocated. WC is best done at home but it can also be done at school during screening campaigns. DC is the next best alternative when WC is not possible and is perhaps more feasible for routine screenings. VI should be abandoned.

A full description of this research is given in paper 1.

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3. Epidemiology of pediculosis

Numerous reports on the epidemiology of pediculosis have been published. These reports generally describe local prevalence rates of pediculosis in school children. Some also investigate the influence of specific characteristics of each child examined in order to identify risk factors for pediculosis. The potential risk factors studied can be divided in three categories: personal characteristics of the child (age, sex, hair type, hair colour and hair length), crowding (class, school, educational level) and SES (profession, educational degree or income of the parents). Only a few studies report incidence rates recorded over a longer period of time. These data are nevertheless important to detect seasonal trends or the influence of social events such as the start of school after a long holiday. Longitudinal follow up is also important to monitor the effect of new management strategies on a short and long term basis.

Studies on the prevalence of pediculosis should be interpreted carefully because there is an enormous heterogeneity in the diagnostic criteria, diagnostic methods and statistical methods used (Table 1). The most accurate screening method should be used in order to obtain reliable results. This means that the screening should be performed at least with dry combing or even better with wet combing. This is discussed in detail in Chapter 2. The complex interaction between several characteristics should be taken into account in the analysis of the results, necessitating the use of the appropriate statistical techniques.

There are currently several gaps in our knowledge about the epidemiology of pediculosis. The following two questions are relevant to the management of pediculosis in Belgium:

- What is the prevalence of pediculosis in schoolchildren between 3 and 12 years of age in Belgium.
- What are the risk factors for pediculosis in this population.
Table 1: Summary of studies on prevalence of pediculosis.

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Sample size</th>
<th>Diagnostic criteria</th>
<th>Diagnostic method</th>
<th>Prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>2005</td>
<td>1370</td>
<td>Nits and/or mobile lice</td>
<td>Visual inspection</td>
<td>61.4%</td>
<td>52</td>
</tr>
<tr>
<td>Korea</td>
<td>2003</td>
<td>7495</td>
<td>Nymphs, lice or viable eggs</td>
<td>Visual inspection</td>
<td>5.8%</td>
<td>54</td>
</tr>
<tr>
<td>Turkey</td>
<td>2005</td>
<td>1569</td>
<td>Nymphs, lice or nits</td>
<td>Visual inspection</td>
<td>16.6%</td>
<td>61</td>
</tr>
<tr>
<td>Turkey</td>
<td>2003</td>
<td>5318</td>
<td>Live or dead eggs or nits</td>
<td>Visual inspection</td>
<td>6.8%</td>
<td>62</td>
</tr>
<tr>
<td>Brazil</td>
<td>2002</td>
<td>884</td>
<td>Nymphs, lice or nits</td>
<td>Visual inspection</td>
<td>35%</td>
<td>63</td>
</tr>
<tr>
<td>India</td>
<td>2002</td>
<td>940</td>
<td>Nymphs, lice or eggs</td>
<td>Visual inspection</td>
<td>16.6%</td>
<td>64</td>
</tr>
<tr>
<td>Jordan</td>
<td>2000</td>
<td>2519</td>
<td>Nymphs, lice or nits</td>
<td>Visual inspection</td>
<td>13.4%</td>
<td>65</td>
</tr>
<tr>
<td>Kenya</td>
<td>1986</td>
<td>1270</td>
<td>Lice or viable eggs</td>
<td>Visual inspection</td>
<td>8%</td>
<td>66</td>
</tr>
<tr>
<td>UK</td>
<td>2000</td>
<td>909</td>
<td>Nymphs or lice</td>
<td>Dry combing</td>
<td>28.3%</td>
<td>5</td>
</tr>
<tr>
<td>Israel</td>
<td>1990</td>
<td>3079</td>
<td>Lice or viable eggs</td>
<td>Dry combing</td>
<td>11.2%</td>
<td>4</td>
</tr>
<tr>
<td>Niger</td>
<td>1985</td>
<td>7360</td>
<td>Nymphs or lice</td>
<td>Dry combing</td>
<td>5.7%</td>
<td>67</td>
</tr>
<tr>
<td>Belgium</td>
<td>2005</td>
<td>6169</td>
<td>Living lice or nymphs</td>
<td>Wet combing</td>
<td>8.9%</td>
<td>2</td>
</tr>
<tr>
<td>Australia</td>
<td>2004</td>
<td>1838</td>
<td>Lice or live eggs</td>
<td>Conditioned combing *</td>
<td>13%</td>
<td>3</td>
</tr>
<tr>
<td>Belgium</td>
<td>2002</td>
<td>677</td>
<td>Living lice or nymphs</td>
<td>Wet combing</td>
<td>16.4%</td>
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<td>Turkey</td>
<td>2003</td>
<td>20612</td>
<td>Live lice or nits</td>
<td>Not specified</td>
<td>3.4%</td>
<td>68</td>
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<tr>
<td>Nederland</td>
<td>2000</td>
<td>2008</td>
<td>Live lice or eggs</td>
<td>Not specified</td>
<td>0.8%</td>
<td>59</td>
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<tr>
<td>Argentina</td>
<td>1997</td>
<td>341</td>
<td>Nymphs, lice or nits</td>
<td>Not specified</td>
<td>81.5%</td>
<td>69</td>
</tr>
<tr>
<td>Australia</td>
<td>1999</td>
<td>456</td>
<td>Lice, viable eggs</td>
<td>Pediculicide combing **</td>
<td>21%</td>
<td>6</td>
</tr>
</tbody>
</table>

* Conditioned combing is another variant of wet combing. The hair is not wetted first and the conditioner is applied on dry hair.
** The hair is first treated with a permethrin 1% formulation and combed with a fine toothed comb.
Original research was performed in order to explore prevalence and the risk factors for head lice in children between 3 and 12 attending nursery and primary schools in Ghent, Belgium.

A total of 6169 children, representing 30% of the total target population, were screened with the wet combing method. Information about personal characteristics of the child (age, sex, hair length, colour and type, class and school) and characteristics of the family (number of children in the family and SES) was collected. SES of the family was based on the person with the highest occupational status in the household. Data were analysed bivariately using \( \chi^2 \) statistics. A multilevel analysis was performed, using software written in SAS.

Live lice were found in 8.9% of the children and another 4.6% had nits without lice.

Bivariate analysis showed a significant association between the presence of head lice and the child’s sex, educational level, hair length and colour, number of children per family and SES. However, a multi-level analysis showed that the child’s class and school had a greater impact on the risk of getting head lice than his or her individual characteristics. The variance at school level was 1.93 (P= 0.011). The variance at class level within schools was 2.58 (P < 0.001) and the level of the different children within classes was 0.59 (P < 0.001).

Some personal characteristics (hair colour, hair length, family size and SES of the family) were significant on the individual level. Children with brown hair have a higher risk for getting head lice than children with other hair colours. It could be assumed that brown coloured lice contrast more in fair, red and black hair and are therefore detected earlier in these hair types than in brown hair. Hair length was also a significant risk factor with longer hair entailing a higher risk. The importance of hair length could be explained by the fact that lice are mainly transmitted by head-to-head contact and subsequently opportunities for transmission occur more frequently in long hair. As far as family size is concerned, children in larger families have a higher risk of being infested. This could be explained because they have multiple siblings that can act as potential sources. Finally, the current study showed that children from families with a lower SES are more at risk of getting lice.

The current research demonstrated that a multilevel analysis is needed to determine the unique impact of each independent variable. This study also showed that clustering of children in groups (in classes and schools) is the most important factor determining the risk of head lice.
The results of this study need to be interpreted with care. A statistical significant association between head lice and several individual characteristics of the child do not necessary imply a causal relationship. Presumably the factors indirectly lead to a higher prevalence because they hamper detection (e.g. hair colour) or treatment of lice (e.g. SES).

A full description of this research is given in **paper 2**.

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4. Treatment

4.1 Treatment of lice

Finding the appropriate treatment for pediculosis is a real challenge. Patients are confronted with a bewildering choice of treatments and often they “cannot see the wood for the trees”. The role of health care workers is to advise parents and patients on the relative value of the available treatment options, based on the best available evidence, taking each patient’s own specific circumstances and preferences into account. Furthermore, the safety profile of the different treatment options should also be taken into account.

The central research question in this field is:

What are the treatment options for pediculosis, what is their value and place and what evidence is there to support their use?

The treatments for pediculosis can be divided into six categories: local chemical treatments, mechanical treatments, systemic treatments, natural treatments, suffocating agents and “household remedies”.

Since the 1940s, most research on the treatment of pediculosis has revolved around natural or synthetic insecticides.21 One of the oldest groups of insecticides are the organochlorines of which DDT is the most notorious member. DDT has been used extensively for the treatment of pediculosis but also in food production. It was banned in 1973 in the USA because of human safety reasons and environmental issues.70 Lindane is another insecticide belonging to the organochlorines. The use of lindane has been forbidden in Belgium since 1997 but this product is still used for the treatment of pediculosis capitis in other countries.32 71 Carbaryl is an insecticide which is available only on prescription in the UK. The most commonly used insecticides for the treatment of pediculosis are pyrethroids and malathion.
In the 19th century flowers of *Chrysanthemum cinerariaefolium* were used for their insecticidal properties. These flowers contain the natural insecticidal product pyrethrin. Soon after the discovery of the chemical structure of pyrethrin, the first synthetic pyrethroid, allethrin was produced. It was not long before other more active pyrethroids were developed, such as d-phenothrin, bioallethrin and permethrin. Pediculicides based on pyrethroids often also contain the synergist piperonyl butoxide. It inhibits mixed-function oxidases and reduces metabolic resistance to pyrethroids. Malathion 0.5% lotion was developed more than 30 years ago. It is an organophosphate which irreversibly inhibits cholinesterases.

In Belgium pediculicides containing malathion, permethrin and bioallethrin (or depallethrin) are available over the counter.

Mechanical treatments are based on removing adult lice and nymphs using a head louse comb. Electric head louse combs and a system connected to a vacuum cleaner (“Lice snatcher”) have been developed but only the Bug Busting method has been tested in clinical trials.

Several systemic treatments have been suggested for the treatment of head lice. Two small clinical trials of limited quality report on the use of the antibiotic combination of sulfamethoxazole and trimetoprim. Rare but severe side effects such as aplastic anemia and toxic epidermal necrolysis have been reported after the use of this compound. This antibiotic should be reserved for the treatment of serious bacterial infections.

Anthelmintic compounds, such as thiabendazole, albendazole and levamisole have been suggested as effective treatments, based on uncontrolled open studies or dubious clinical trials. Side effects such as cutaneous reactions, hematologic abnormalities and gastrointestinal problems have been reported. These agents should be used for severe parasitic infestations and not for pediculosis since safer, local treatments are available. Recently ivermectin has been suggested as a treatment option for pediculosis. However, it is not recommended for children younger than 5 years of age or less than 15 kg in weight. Furthermore, the safety and efficacy of this product in the treatment of pediculosis has not been established. For these reasons, ivermectin should not be used in the treatment of pediculosis.
Over the last decade there has been an increasing interest for the insecticidal properties of essential oils and natural compounds. Essential oils such as tea tree oil, *Eucalyptus globulus* leaf oil, *Eugenia caryophyllata* oil, *Lippia multiflora* oil, have shown some pediculicidal and ovicidal activity in vitro.  

Two small clinical studies attribute pediculicidal activities to extracts of *Annona squamosa* seed and henna. A natural remedy containing coconut and ylang-ylang oil had the same effectiveness as a classic pediculicide in an open clinical trial.  

Essential oils and natural compounds are extracted from plant material and usually contain many different chemical constituents. There is little control on the quality and composition of these oils. Their composition may vary according to the manufacturer or batch. These products are also at risk of contamination, for example with pesticides used during the cultivation of the plants. Little is known about the mechanisms responsible for the pediculicidal effect of essential oils and other plant extracts.  

Tee trea oil was recently shown to inhibit acetylcholinesterase which is also the mode of action of malathion. More information about the mechanism of action and safety profile of these products is needed before they can be assessed in clinical trials. Until then, these products should not be used in the treatment of pediculosis.

Another approach to the treatment of head lice is based on the hypothesis that lice can be suffocated with local agents. One study reported astonishing results with Cetaphil ® cleanser (a gentle soap to clean the face) but raised ethical concerns and was heavily biased. A second study found that the cure rate with dimethicone 4% lotion was 70% which was comparable to the cure rate of classic pediculicide. This treatment might be valuable if the results are confirmed in future trials.

Finally household remedies such as oils, hair gel, mayonnaise or petrolatum have been cited in literature. Even dangerous products such as kerosene or gasoline are mentioned. An in vitro study demonstrated that household remedies such as vinegar, isopropyl alcohol, olive oil, mayonnaise, melted butter and petroleum jelly are not capable to eliminate head lice efficiently.

A treatment for pediculosis should be effective and safe. When evaluating the effectiveness of treatments, the best available evidence, which is a systematic review
in first instance or good quality RCT’s, should be consulted. A major problem in the treatment of pediculosis is the lack of good quality RCT’s and traditional literature reviews.\textsuperscript{103} There are no RCT’s of good quality on the use of home remedies, natural treatments, systemic treatments and mechanical treatments except Bug Busting.

Two systematic reviews, mainly on the effectiveness of pediculicides, have been published. The first by Vander Stichele et al.\textsuperscript{104} concluded that sufficient evidence proved the effectiveness of permethrin alone and that more evidence was needed for treatments such as malathion and carbaryl. Pyrethrines were assessed as not sufficiently effective.\textsuperscript{104} However, the criteria to assess the quality of the clinical trials were developed post hoc and not a priori, as acknowledged by the author.\textsuperscript{105}

A second systematic review by the Cochrane collaboration concluded that effectiveness was proven for permethrin, malathion and synergized pyrethrins. However, this review included only 3 clinical trials on pediculicides. Several methodological concerns were raised regarding this review. The 3 accepted trials were conducted in developing countries, involving populations that do not reflect the patients in a developed country. The review also ignored 2 trials referenced in the systematic review by Vander Stichele. Furthermore, the selection of trials and the assessment of quality was biased by a high number of personal communications.\textsuperscript{103}

As far as safety of the different treatments is concerned, pyrethroids seem to have a favourable safety profile. Natural pyrethrins can elicit local side effects such as skin irritation, rash, redness and swelling. This natural plant extract should not be used in patients allergic to chrysanthemums, ragweed and other related plants because of a possible cross reaction. Permethrin on the other hand does not cause allergic reactions in people with plant allergies. In a postmarketing surveillance study of permethrin 1% crème rinse, 2.2 adverse events per 1000 treatments were reported. All recorded adverse events (such as oedema, erythema, hypoesthesia and pruritus) were mild.\textsuperscript{106}

Malathion is also regarded as a safe product with only minor adverse events (scalp irritation and conjunctivitis) reported but some concerns have been raised. Alcoholic lotions containing malathion are potentially flammable. Mutagenic and carcinogenic effects have been found in vitro and in animal studies\textsuperscript{107} but these effects have not been reported in humans.
Severe adverse events have been associated with the use of lindane. These include neurological effects such as dizziness, seizures, headache and paresthesia and even some deaths have been reported.\textsuperscript{108} Lindane is no longer in use in Belgium.

One case-control study found a statistical significant association between acute leukaemia and the use of home insecticides, garden insecticides and insecticidal treatment for pediculosis.\textsuperscript{109} However, these results are probably influenced by a “recall bias” and should be confirmed by further research.

In view of the emerging resistance and to limit the exposure to insecticide, it is sensible to avoid repeated treatment with pediculicides. If chemical treatments are ineffective it is advisable to consider a mechanical treatment option such as Bug Busting.

Until now Bug Busting has been studied as a treatment option in 4 clinical trials, of which the first was a pilot trial and the second, an open trial on efficacy.\textsuperscript{77,110} A third, pragmatic trial found that the cure rate with Bug Busting was only 38\% which was significantly lower than the cure rate of 78\% in the group treated with malathion.\textsuperscript{76} Finally, in a recent effectiveness trial with an improved version of the Bug Buster Kit, a significantly greater proportion was cured with the Bug Buster Kit than with over the counter pediculicides (57\% versus 13\%).\textsuperscript{55} The overall quality of this study is good. A possible bias could be that no information is given on the number of children who volunteered for this study but were finally not included. This might have introduced an inclusion bias in favour of Bug Busting.\textsuperscript{111}

As an overall conclusion it can be stated that there is insufficient evidence to support the use of home remedies, natural products and systemic treatments. The effectiveness of pediculicides and Bug Busting has been demonstrated in clinical trials. The success rate of these treatments will depend the patient’s (or rather his/her parents) preference which might be influenced by financial issues, time investment, motivation, concern about toxicity, application skills needed and consideration of the environmental consequences.

4.2 Resistance to pediculicides

Another decisive factor for the success rate of chemical treatments is the pattern of local resistance.

DDT was formerly used for head louse control but widespread use of the product led to world-wide resistance. Similarly, lindane has become ineffective in many parts of the world due to extensive use.

Clinical trials with permethrin showed a cure rate of 99% back in 1986 when the product was first introduced. Less than 10 years later in vitro studies from Israel and the Czech Republic demonstrated that lice collected from local school children were significant less sensitive to permethrin compared to a fully susceptible reference strain. Since then, varying levels of permethrin and/or pyrethrin resistance have been reported in France, Argentina, the UK, Australia, the USA and Denmark.

Similarly, cure rates with malathion were close to 100% in the early 1990’s but recently resistance to malathion has been reported in the UK, Australia and Denmark.

Resistance is usually monitored with bioassays. In 1981 the WHO issued a protocol for resistance testing in body lice and head lice. According to this protocol, groups of 10 to 20 adult lice are exposed to a pediculicide impregnated filter paper. After the exposure time, which depends on the tested pediculicide, lice are transferred to clean sheets and incubated for 24 hours before counting mortality. Problems with the WHO protocol, such as difficulties to hold the lice for the required time, have lead to many different versions of the filter paper assay. Some groups apply time-mortality bioassays in which mortality is recorded in function of exposure time, while others use dose-mortality assays in which lice are exposed for a fixed amount of time but replicates with different concentrations are done. Protocols also differ in the life stages used (first instars, adults only, adults and large nymphs), the fully susceptible reference strain used (laboratory reared body lice versus insecticide susceptible head lice), exposure time (1 hour versus 2 hours) and preparation of filter paper disks. Recently, a topical application procedure in which a fixed amount of fluid is applied per louse has been described. According to the authors, a wider range of resistance levels can be
measured using this method. They also suggest that it is an easier and faster procedure than the filter paper method. However, more studies comparing the topical application method to the filter paper method are needed to examine the correspondence between the two methods.\(^{113}\)

The heterogeneity in susceptibility assays makes it impossible to compare resistance rates between different countries. Nevertheless, resistance has been recorded in several countries.

In 1994, resistance to permethrin was documented in head lice in Israel, only 2.5 years after the introduction of permethrin to the Israeli pediculicide market.\(^{121}\)

In Argentina, a sample of lice, collected from children in different schools in Buenos Aires, showed resistance to permethrin, however with considerable variation in the resistance ratios according to the school where the lice originated from. There was cross resistance to deltamethrin and sumithrin, two other pyrethroids, but not to carbaryl.\(^{122}\)

Permethrin resistant lice have also been detected in the United States. This sample was still susceptible to malathion, a product that is only available on prescription and is available on the US market since 1999.\(^{116}\)

In vitro studies on head lice collected in Bath and Bristol showed double resistance to both malathion and permethrin. Head lice from these samples remained fully sensitive to carabaryl.\(^{114}\)

In a later study, head lice from four regions in the UK were found to be resistant to permethrin and malathion. Head lice collected in Leeds were also resistant to carbaryl.\(^{124}\)

Susceptibility tests by Hunter et al demonstrated substantial variability in susceptibility to malathion, pyrethrum an permethrin between different schools in Australia.\(^{115}\) Permethrin and malathion resistance has been demonstrated in samples of head lice in Denmark.\(^{117}\)

In general, there are two major resistance mechanism: target-site modification and enzyme-based detoxification. In target-site modification, the pediculicide no longer binds to the target site.

In enzyme-based detoxification the pediculicide is degraded before it exerts its effect. Monooxygenases, esterase and glutathione S-transferase (GST) are the major enzyme groups responsible for enzyme-based resistance to organophosphates (such
as malathion), carbamates (such as carbaryl) and pyrethroids (such as natural pyrethrum, phenothrin and permethrin).

Most of the research in head lice has focussed on mechanisms involved in pyrethroid resistance.

In a filter paper assay by Picollo et al., head lice were found to be resistant to permethrin and cross resistant to deltamethrin, β-cypermethrin and d-phenothrin but not to carbaryl. The addition to the permethrin impregnated filter papers of piperonylbutoxide (PBO) a mixed function oxidase inhibitor, partially reversed the permethrin resistance. Triphenylphoshate, a carboxyesterase inhibitor also reversed permethrin resistance but to a lesser extent than PBO. The authors concluded that enhanced metabolism is involved in pyrethroid resistance but the substantial degree of resistance remaining after synergism suggests the presence of other mechanisms.73

The same group measured the activity of monooxygenases in a sample of permethrin resistant head lice, using 7-ethoxy coumarin (ETOC) as a substrate. The rate of deethylation of ETOC by monooxygenase was determined by measuring fluorescence. A positive relation was found between enzyme activity and the level of permethrin resistance.125

In a sample of Israelian head lice, there were indications of a GST based DDT resistance. This mechanism confers secondary resistance for some organophosphates but not for pyrethroids. The authors could not find an association between pyrethroid resistance and an amplified or elevated esterase system. Monooxygenases only had a small effect on pyrethroid resistance.123

Permethrin resistance was demonstrated in lice collected in Florida and Massachusetts. Pre-treatment with PBO resulted in a significantly faster mortality response in the Massachusetts strain but not in the Florida strain, indicating that the oxidative metabolism serves as a permethrin resistance mechanism in the former strain but not in the latter.126

Reduced neuronal sensitivity or “knockdown-resistance” is a form of target-site modification and is a common resistance mechanism for both DDT and permethrin resistance and has been documented in several species. It is unaffected by
synergists that inhibit insect esterases and monooxygenases. It is caused by reduction in the sensitivity of the insect nervous system to pyrethroids.

Genetic analyses showed that this type of resistance is tightly linked to the para-orthologous voltage-sensitive sodium channel α-subunit gene. Voltage gated sodium channels are transmembrane proteins that regulate sodium influx into the cell, causing depolarisation of the cell membrane and propagation of action potentials. Pyrethroids bind to these proteins, causing a permanent influx of sodium ions and a prolonged depolarisation of the neuronal cell membrane eventually leading to paralysis.

These sodium channels consist of an α subunit and two β subunits. The α subunit is thought to have 4 domains, each consisting of 6 transmembrane segments. Through molecular cloning and sequencing, two point mutations (T929I and L932F) have been located in the IIS5 transmembrane segment in permethrin-resistant lice collected in Florida and Bristol.\(^\text{126}\)

In a later study, permethrin resistance was again confirmed and a strong correlation was found between the presence of T929I and L932F mutations and permethrin resistance was found.\(^\text{116}\) In Denmark, 95% of the tested permethrin resistant lice had both T929I and L932F mutation.\(^\text{117}\)

These two mutations and the more recently detected D11E and M850T mutations are potential genetic factors responsible for kdr type resistance.\(^\text{127}\)

The mechanisms conferring to malathion resistance have only recently been investigated. Possible mechanisms are reduced target site sensitivity but also enhancement of metabolism by cytochrome p450 monooxygenase, GST and phosphotriesterases.

Malathion resistant head lice from Bristol were used to determine which mechanisms are important in malathion resistance. Bioassays, using S,S,S-tributylphosphorotrithioate (DEF) as an esterase inhibitor and PBO as a monooxygenase inhibitor showed that the addition of DEF increased the toxicity of malathion but not of permethrin. PBO synergised neither malathion or permethrin. These findings suggest that esterase play an important role in malathion resistance and that kdr is important in permethrine resistance.
General esterase activity and GST activity was elevated in the resistant strain. Phosphotriesterase and acetylcholinesterase activity and acetylcholinesterase sensitivity were not changed. The general esterases in resistant strains showed significantly higher affinities and rates of hydrolysis. Electrophoresis showed two prominent bands within the general esterases and the activity of these two isoenzymes was greatly elevated in the resistant strain. Resistant lice had a 13.3 fold higher malathion cholinesterase activity compared to susceptible lice. It is hypothesised that an elevated level of malathion cholinesterase activity with possibly a unique isoform that has an elevated hydrolysis activity is the major cause for malathion resistance. There was no difference in acetylcholinesterase activity or sensitivity, indicating that altered target site is not likely to be involved in malathion resistance.  

From the reports discussed above, it seems that resistance to permethrin and malathion is widespread and that resistance to carbaryl is starting to emerge. The pattern of resistance varies from region to region and even from school to school. It seems that the resistance pattern in a region is influenced by the pediculicides used in that specific region. Pediculicides might work in one region and can be totally useless in another.  

Epidemiological methods need to be developed to screen for resistance in small health care areas and to guide regional adaptation of treatment plans.

The available research suggests that monooxygenases are partially responsible for permethrin resistance. This type of resistance can be overruled by the use of PBO, a synergist that inhibits mixed function oxidase. However, assays also suggest that another mechanism, more specific knockdown-resistance or kdr plays an important role in pyrethroid resistance. A strong correlation has been found between permethrin resistance and point mutations T929I and L932F. In contrast to this, target-site modification does not seem to play a role in malathion resistance. Recent research suggest that an elevated malathion cholinesterase level is the major mechanism in malathion resistance.

Reliable, fast and cheap detection methods are needed for the repeated epidemiological assessment of local resistance patterns, based on bio-assays and if possible, on genetic screening for mutations in head lice.
Resistance to pediculicides can no longer be ignored and will probably become more and more important. One way to overcome insecticide resistance is to develop new pediculicides. However, history has illustrated that these products have a relative short life span. Mechanical methods such as Bug Busting, are not influenced by resistance and are therefore a valid treatment option, especially in regions with high resistance.
4.3 Removal of eggshells

The presence of eggshells (with or without viable eggs) poses several problems. The first problem is that chemical treatments for pediculosis should have optimal pediculicidal but also ovicidal properties in order to effectively control pediculosis. But the latter is often their downfall. Most formulations are not sufficiently ovicidal and should be repeated regularly to kill the newly hatched nymphs.\(^{29,112}\) Even if a patient is successfully treated, the empty eggshells can remain for a long time in the hair because they are firmly stuck to the hair and difficult to remove. In these circumstances, the presence of obvious nits is not only a cosmetic problem and is sometimes mistaken for an active infestation leading to unnecessary treatment.\(^{128}\)

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<tr>
<th>A literature search was started, based on the following questions:</th>
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<td>How are eggshells attached to the human hair?</td>
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<tr>
<td>Which products are efficacious for the removal of eggshells from human hair?</td>
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The egg laying process has been extensively studied in body lice. Egg laying by head lice shows great resemblance to the process in body lice. The egg and its membranes develop in the ovarioles of the female louse. They are separated from the oviduct by a plug of tissue. First, the louse threads a hair between the gonopods. Then an adhesive substance is secreted by the glue glands. The substance fills the oviduct and is spread around the human hair, forming a tube. Then the plug of tissue breaks and the egg is released into the oviduct and pushed into the adhesive substance. The substance sets and forms a solid tube or cylinder around the hair which extends into an eggshell (which is also known as a “nit”) surrounding and protecting the egg.\(^{129}\) The distal end of the egg consists of several domed elements and is called the operculum. This structure is not covered with the adhesive substance and in vitro experiments using body lice eggs suggest that the operculum functions as a respiratory opening.\(^{129}\) Usually the eggshells are oriented with the cylinder towards the hair root and the operculum pointing towards the tip of the hair. Empty eggshells, eggshells containing a viable egg or embryo and eggshells containing a dead egg/embryo can be found in the hair of an infested person. At the beginning of embryonic development only patches of cells are visible.\(^{129}\) Towards the
end of the development several structures such as the head, the red eye spot and the limbs can be distinguished. The operculum is clearly visible (Fig. 3).

![Image of a viable nit](http://www.hsph.harvard.edu/headlice/photos.html)

Viable eggs are shiny and tan to brown coloured. Dead eggs are shrivelled and are dark brown or black. The empty eggshells whiten and become translucent and the operculum is gone. A microscope is needed to accurately distinguish between the three types of eggshells (Fig. 4).

In the past a rule of thumb was formulated to distinguish viable from non-viable eggs with the naked eye. It was assumed that eggs were always laid close to the scalp. Eggs located further than 1 cm away from the scalp were presumed to be dead. Since hair grows at a rate of approximately 1 cm per month, eggs located further than 1 cm from the scalp are older than 1 month and non-viable. However, eggs can also be laid further away from the scalp, for example when long hair touches the
The rule of thumb that nits further than 1 cm from the scalp are dead or empty is thus not correct.

Several authors have tried to unravel the composition of the eggshell. Histochemical examination of the adhesive substance using the glue glands dissected from living female lice revealed that the adhesive mainly consist of proteins. This finding was confirmed by Burkhart et al. who performed pyrolysis-gas chromatography and mass spectrometry on the solid nit cylinders. This study revealed a high relative abundance of components derived from phenylalanine, tyrosine, tryptophan and glutamic acid. The same authors investigated whether products such as vinegar, acetone, vodka, bleach, all purpose degreaser and petrolatum facilitated the removal of nits in vitro. Only bleach, vodka and vinegar assisted mildly but were not therapeutically efficacious. Mumcuoglu et al. report that acid shampoos, 5% acetic acid, conditioners and vegetable oils are effective in detaching eggs from the hair. However, none of these authors describe how they measured the effect of the studied products.

In a small un-blinded clinical study beneficial results were demonstrated with a nit removal system containing a formic acid 8% cream rinse and metal comb. The control site was only combed with a plastic comb. However, difference in the type of combs used could account for a better result in the treated site. Thorough in vitro and in vivo studies are lacking to support the use of products to facilitate nit removal. Nevertheless, home remedies such as vinegar and the formic acid cream rinse are cited over and over again in traditional literature reviews.

The central issue in this field of research is the quest for products that facilitate the removal of nits in vitro and in vivo.

A first step in this quest is to find a procedure to objectively measure the force needed to remove nits from the human hair. Because no such procedure was described in literature, we developed a device for in vitro measurements of the force needed for nit removal.

A small metal cylinder was attached to a force transducer. A hair with a nit was put with its scalp end through the metal cylinder and knotted to a bent needle connected to a surgical thread. The thread was attached to the axis of a slow-spinning electrical motor. The measurement procedure started when the motor was activated and
began pulling the hair through the cylinder. At the point where the nit was halted by the metal cylinder, force started to build up, until the nit cylinder lost grip on the hair and the hair began sliding through the immobilised nit (Fig. 5). The device was calibrated and tests showed that the method had an acceptable level of precision. The force from the force transducer was recorded with a pen recorder, producing graphs of developed force as a function of time. The following parameters were determined: 1) the first peak in the plot (Fpeak), 2) the average force (Fav) and 3) the maximum force (Fmax).

![Diagram of the device to measure the force needed to remove a nit. The proximal end of the hair is slid through the metal cylinder that is attached to the force transducer. The proximal end is knotted to the bent needle of a surgical thread that is attached to the motor. The hair with the nit starts to slide through the metal cylinder when the motor is turned on. The metal cylinder holds the nit back, and the force to remove the nit is measured.](image)

A total of 104 hairs from 18 infested children were cut as close to the scalp as possible. Only single nits attached 17 mm from the proximal end of the hair were used for technical reasons. The distal end of the hair was cut 20 mm behind the nit. The diameter of the hair, the distance of the nit from the scalp end of the hair and the length of the nit cylinder were also determined (Fig. 6). A Spearman’s rho correlation coefficient was used to explore correlations and the Kruskal-Wallis test was used to compare medians of multiple groups.
The mean ± SEM of Fpeak, Fav and Fmax was respectively $66 \pm 3.7$, $51 \pm 3.1$ and $130 \pm 5.3$ mN ($n=93$). There were no significant between-patient differences in the measured forces. A positive correlation was found between all three force parameters and the length of the nit cylinder, a negative correlation was found between Fmax and the distance of the nit from the scalp end side of the hair. There was no correlation with the diameter of the hair.

The device described above is easy to handle and cheap to construct. Furthermore, it proved to be a feasible and reliable method to measure the force parameters that determine the difficulty or ease with which nits can be removed from human hairs. This procedure was further optimised to improve data processing and was used to evaluate the efficacy of several products to facilitate the removal of nits from human hairs.

Hairs were obtained from 6 children between 7 and 11 years (average age 9). The hairs of patient 1 and 2 were divided into 13 equal groups of approximately 25 hairs. These groups were used for the measurements in batches 1, 2 and 3. For the 4th batch, 7 equal groups were created with the hairs of patients 3 and 4. Finally, the 5th batch consisted of five equal groups containing hairs of patients 5 and 6.

Within one batch, the hairs from two patients were divided so that all groups contained more or less the same number of hairs and that there were no differences in distance of the nit to the proximal end of the hair or length of the nit cylinder.
The products tested within one batch can be compared because the groups within one batch were very similar. Batches 1, 2 and 3 can also be compared with each other because hairs from the same patients were used. They cannot be compared to batch 4 or 5 because hairs from different patients were used.

In the first batch, a short treatment with commercial nit removal products and ordinary conditioner was tested. The commercial nit removal products, available in Belgium or The Netherlands, are basically conditioners with one or more additives that are supposed to facilitate nit removal.

One group of hairs was left untreated. The other groups were treated respectively with Shampoux Balm Activ, Para Balm, Neetex and ordinary conditioner. The hairs were treated according to the instructions on the package insert. The hairs were first wetted with luke-warm running tap water before the product was applied. The product was left on for 10 minutes and rinsed before testing.

In the second batch the effect of formic acid (FA) solutions with different pH values was explored. FA solutions with a pH of respectively 2, 3, 4, 5 and 6 were prepared by changing the ratio of sodium formate to FA, and were tested on five groups of hairs. A sixth group was used to test the effect of the vehicle, which was pure deionized water with a measured pH of 5.4. All groups were immersed in the FA solution or pure deionized water for 10 minutes and tested immediately, without rinsing. These groups were compared to the group of untreated hairs from the first batch.

In the third batch, the effect of FA in a gel vehicle was tested. One group of hairs was treated with the blanco gel (vehicle) and a second group with a gel containing 4% FA. The effect of these substances was compared to the untreated hairs (from batch one) and hairs treated with deionized water (from batch two).

In a fourth batch, we tested the effect of the consistency of the HPMC gel, but also of an application with almond oil and a long application of conditioner.

A first group was left untreated and a second was treated with deionized water, as described above. The third and fourth groups were treated as previous with a blanco 2% HPMC gel and a blanco 3% HPMC gel. In the sixth group almond oil was applied for 10 minutes and then rinsed under luke warm tap water. In the seventh group, the
same oil was left on the hair during force measurement. In an eight group the ordinary conditioner was applied on the hair and left on during force measurements. Finally the fifth batch was used to explore the effect of a long application of conditioner versus a short application. One group was left untreated; the hairs of group 2 and 4 were treated for 10 minutes with respectively the ordinary conditioner and a commercial nit removal product (Para Balm). Groups 3 and 5 were treated with the same products but the hairs were not rinsed.

Data were analyzed using SPSS software (version 12). The Kruskal-Wallis test was used to compare medians of multiple groups and the Mann-Whitney test was used to compare medians of two groups. The threshold for statistical significance was at $P < 0.05$.

The measurements in the first batch showed that treating the hairs with a commercial nit removal product, ordinary conditioner or a soak in deionised water significantly reduced the Fav and Fmax (Fig. 7A). In the second batch with FA solutions, the Fav was only significantly reduced in the group treated with deionised water (Fig. 7B). Fmax on the other hand was significantly reduced in all treated groups. In the third batch both Fav and Fmax were reduced in the groups treated with the pure HPMC gel and HPMC gel with 4% FA but there was no difference when compared to a soak in deionized water. (Fig. 7C)

In the fourth batch, Fav and Fmax were reduced in the group treated with deionized water and almond oil left on the hair. Fmax was also slightly reduced in the group treated with 3% HPMC gel. The continuous application of ordinary conditioner strikingly reduced the measured forces (Fig. 7D).

Finally the measurements in the fifth batch revealed no difference between the commercial product and the ordinary conditioner. The continuous application of either the commercial product or the ordinary conditioner resulted in a greater reduction of Fav and Fmax than the short application. (Fig 7E)

A first observation in the current research was that deionized water significantly reduced the force needed to remove a nit. LaTorre et al. observed that a soak in deionized water reduces the friction coefficient of a hair. The water probably acts a lubricating layer and reduces the friction between the hair and the nit. A second observation was that ordinary conditioner also facilitated the nit removal. A short application of conditioner was less efficacious than the continuous application.
Fig. 7: Box plots of Fav in the different treatment groups. A) Different commercial nit removal products and ordinary conditioner, short application time. B) HPMC gel with and without FA. C) Solutions of FA with different pH. D) Almond oil long and short application time, pure HPMC gel in different consistency, ordinary conditioner long application time. E) Ordinary conditioner and commercial nit removal product in long and short application time.
* SSD from untreated with P < 0.05. ** SSD from untreated with P < 0.001
of the conditioner. It has been demonstrated that a conditioner acts as a lubricant and decreases friction. Probably the hair is surrounded by a thicker layer if conditioner is left in place during the force measurements.\(^{136}\) We also observed no difference between ordinary conditioner and commercial nit removal products. Furthermore, the addition of formic acid to deionized water did not reduce the forces needed to remove the nit compared to pure deionised water. On the contrary, forces were higher in formic acid solutions with pH 4, 5 and 6. It has been observed that the friction coefficient in damaged hair is higher than in undamaged hair.\(^{136}\) It is not unlikely that formic acid damages the hair, hampering the removal of nits.

In the research described above, the efficacy of several products was determined by applying each product to individual hairs. The force to remove a nit was measured using a device which consisted of a metal cylinder attached to a force transducer. There are however some differences between this in vitro setting and clinical practice. Products are usually applied to the whole scalp and not to individual hairs, probably putting a different amount of product on each hair. Furthermore in daily practice a nit comb is used to remove nits, pulling at several nits at a time. It is not known if the in vitro research is representative for the in vivo setting. For this reason, clinical trials are also needed to assess the effectiveness of the tested products.

This research suggests that the continuous application of an ordinary conditioner significantly enhances nit removal. Furthermore, it is a user friendly and non-toxic product, already commercial available. The clinical relevance of this finding needs to be confirmed by in vivo tests.
A full description of this research is given in **paper 3 & 4.**


5. Management of pediculosis

In the management of pediculosis, three questions seem important:

1. Who should be involved in the management of pediculosis
2. What is the role of each partner?
3. How can the strategy be implemented?

Several policies have been proposed for the management of pediculosis. Control strategies with the school nurse in a key position have been promoted in the older literature on the subject. In this type of policy, the school nurse is responsible for the spread of information, detection, follow up of treatment and prevention. The prevention strategy consists of regular screenings at school and the “no-nit policy”. Regular screenings (at least 3 times a year) are advised because they supposedly facilitate early detection. The no-nit policy means that a child is excluded from school as soon as head lice are found. Children are not allowed back to school until all eggshells or nits are removed because they are regarded as a source of potential reinestation and may cause confusion in the diagnosis. This type of control strategy has received a lot of criticism because the responsibility for pediculosis rests entirely on the shoulders of the school nurse. It has not been demonstrated that regular screenings actually reduce prevalence. Data are also lacking to substantiate the benefits of a no-nit policy. Furthermore, exclusion from school (which might be prolonged in some cases) disrupts the educational process.

More and more examples of a “whole-school approach” or community approach are beginning to appear in the literature. These models start from the principle that the management of pediculosis is a concern of the whole community. Children, parents, school nurses, teachers, school administrators, pharmacists and physicians should be involved. Everyone should join forces to create an open, non-stigmatising atmosphere in order to keep pediculosis manageable.
Parents play a key role in the management of pediculosis because detection and treatment is mainly their responsibility.\textsuperscript{142} The containment of pediculosis starts with the accurate and early diagnosis of lice \textsuperscript{130} but many parents neither possess the necessary knowledge nor sufficient skills.\textsuperscript{143} To diagnose head lice, one has to know what lice look like and use the most accurate method to find them. One way to improve the diagnostic capacity of parents could be by getting them into the habit of weekly checking their children\textsuperscript{8}, preferably by wet combing\textsuperscript{143} because this technique is the most accurate diagnostic method currently available and is easiest to do at home.

Treatment is also an important task for parents to undertake. They should be accurately informed about the treatment options and be free to choose the option that best fits their setting and beliefs. This policy improves compliance and diligence in adhering to the therapy protocol.\textsuperscript{144} Parents are often confronted with treatment failure which causes anger, frustration and disappointment. There are many reasons for treatment failure such as reinfestation,\textsuperscript{7,112,145,146} incorrect application of pediculicides,\textsuperscript{7,112,145,146} use of ineffective pediculicides,\textsuperscript{146} incorrect implementation of wet combing, resistance to pediculicides\textsuperscript{7,112,146} or incorrect diagnosis.\textsuperscript{146} Improper use of pediculicides includes excessive dilution, overuse and prophylactic use of pediculicides.\textsuperscript{130} Resistance is caused by pediculicide residue on the hair, exposure of lice to sublethal doses, inadequate concentration of active ingredients in products\textsuperscript{87,145} and unnecessary treatments.\textsuperscript{10}

The role of the school nurse and others SHD staff is to support the parents in the battle against head lice by giving them correct advice in a non-judgemental way.\textsuperscript{142} The advice must be given in a way that is understandable for all parents using easily accessible tools.\textsuperscript{141} School nurses are also an important source of information for teachers.\textsuperscript{147} The transmission of information will be more effective if an open relationship based on trust is established with the parents.\textsuperscript{148} The screening of a whole school is labour-intensive and requires a proper organisation.\textsuperscript{141} There is no proof that regular screening of the whole school will result in a lower prevalence.\textsuperscript{130,139} However, mass screening can be important to create an open atmosphere about the subject. Furthermore, it can be the ideal pretext to involve parents into the management of pediculosis in their community and educate them about correct screening methods for pediculosis.\textsuperscript{1,139} One yearly
screening is also a valuable tool to monitor the effect of pediculosis management programmes. SHD staff most often have contact with families, school administrators, teachers, physicians and pharmacists and this department could be the ideal partner to coordinate the management of pediculosis in a school community and establish a policy.

Teachers can make pediculosis discussable and can help remove the stigma by teaching children about lice. Furthermore, they can reach the parents through their children by setting project work which involves parents. It is also important that teachers are correctly informed about pediculosis because parents often turn to them for advice about pediculosis.

Pharmacists are in the ideal position to give advice on the type of products that are available and how and with what frequency they should be applied. Physicians are often not the first person patients turn to for advice. Patients often try several treatments before seeking medical advice. But when patients seek medical advice it is important that physicians can explain and perform the correct method to diagnose lice. Furthermore, they need to be up to date about the recent evolutions in the treatment of pediculosis. It is their task to prescribe the safest and most effective treatment for pediculosis and supervise the treatment.

A survey in the UK demonstrated that there was a lack of knowledge about treatment and prevention of pediculosis among primary health care professionals and pharmacists, even after the distribution of guidelines. The authors suggest that the lack of knowledge could contribute to ineffective control of head lice infestations and that greater effort is required to educate these professionals.

Last, but not least, local authorities and central government also plays a crucial role in the management of pediculosis. There should be a strict control on the labelling of products that claim to kill head lice. Only products with proven efficacy and effectiveness should be permitted for sale in pharmacies. The government is also responsible for the distribution of correct, understandable evidence-based information through channels which are readily accessible for the general public because an effective management can only be established if all professionals give accurate and consistent treatment advice.
There are several ways to implement a whole-school or whole-community approach. One model describes how a long-term follow-up strategy is organised after an initial elimination programme.

In a first phase, all health care staff received information about pediculosis. Subsequently, all children within the community were screened in a standardised way by trained nurses, in order to assess the baseline prevalence. During the next 12 months public awareness was raised and health care workers, education staff and social services were further educated about pediculosis. During this period an “elimination day” was prepared. The aims of this day were to increase the knowledge about head lice amongst the general public and in particular parents, to reduce the level of infestation and to transfer responsibility of hair care from school nurses back to parents.

In order to get full cooperation, parents were contacted several times through letters and home visits. Short before the elimination day parents were reminded to check the hair of all family members on the elimination day and to treat if necessary.

In the second phase a long term follow up strategy was organised. This strategy consisted, amongst others, of ongoing staff training, education and advice to parents and schools and annual assessments of prevalence.

With this model prevalence rates (defined as signs of past and active infestation) and incidence rates (defined as signs of active infestation) were reduced, but the effect of the initial campaign seemed to fade over the years. The project was welcomed by all staff and parents and reduced dissatisfaction caused by pediculosis.60

Another model is the Bug Busting ‘whole-school approach’. In Bug Busting, the hair is first washed with a shampoo before combing it with a specific head louse comb and a conditioner, as described earlier. The necessary reusable combs and instructions on how to perform the method are packed in one kit which can be bought in the pharmacy. In the Bug Busting programme it is emphasised that a louse needs to be detected to prove active infestation and Bug Busting is promoted as the method of choice for detection. The programme is promoted in school and children take the message home to their parents, encouraging them to do a coordinated family check on a predetermined date, a Bug Busting day. Three Bug Busting days are held every year in the UK.
A whole-school approach, in which all families participate in the programme, has been applied in several projects. These projects illustrate how families can become proficient in detection and eradication of lice through a combination of the use of the Bug Buster kit, an educational programme and regular Bug Busting day. It empowers most families to gain control of head lice, giving health care providers more time to give additional help to the minority of cases that actually need hands-on help. Furthermore, in one project a reduction in the cost of head louse treatment was observed after the implementation of a Bug Busting programme.  

Another example of a whole school project is the wet combing campaign that was organised in Ghent to test the feasibility and acceptability of a structured community approach to control epidemics in primary schools. The project involved 677 children aged 3-11 years, from 3 different schools. A joint meeting of teachers, school health and community representatives discussed the project strategy. A co-ordinated programme was set up, using ‘community-orientated primary care’ methodology, with the objective of involving the community and empowering the target population. It was aimed at children, parents, and school, health and community care staff. The prevalence of active infestations was 13% and 19.5% in two schools. Parents received treatment advice allowing them to choose insecticide medication or repeated wet combing. Seven days after the initial screening families of positive children were visited by an empathic home worker who gathered information on past and current experience with head lice, and assisted with the chosen treatment if explicitly asked. 85% of the children who were found positive at the initial screening were checked again 14 days later. Only 51% were cured at day 14. It was found that a wet combing screening campaign, followed by a home visit to positive cases on day 7 and a follow up screening on day 14 was feasible and not grossly expensive. However, it is stressed that school efforts need to be combined with community efforts.  

Finally, the “Head louse forum”, organised by the government in Flanders, is another example of the implementation of an evidence-based policy. Representatives of several organisations such as school health departments, parents’ associations, child welfare, youth health care services, general practitioners’ association and the pharmacists’ federation took part in this forum. This initiative
resulted in a website (http://www.wvc.vlaanderen.be/luizen/) in which information about the diagnosis, treatment and prevention of head lice is summarised for use, not only by the general public but also for health care professionals.
Part III Scabies
1. Introduction scabies

Since ancient times, it has been known that scabies is caused by a tiny organism.\textsuperscript{154} It is said that scabies is the first disease for which a cause was found.\textsuperscript{155} In 1687 Giovanni Cosimo Bonomo described and drew the scabies mite in his famous letter to Francesco Redi. It was not until the mid nineteenth century that the medical world also accepted this hypothesis, thanks to experiments by Ferdinand von Hebra.\textsuperscript{154, 156}

The human scab mite, \textit{Sarcoptes scabiei} var. \textit{hominis}, is an obligate parasite of human skin.\textsuperscript{157} Female mites are about 400 µm long and 300 µm wide and are twice the size of males. On microscopic examination, the mouth parts and four pairs of legs are usually distinguishable.\textsuperscript{16} Scabies mites are very host specific, meaning that they do not readily infest other hosts. However, cross-infestations are possible but do not frequently occur and are probably self-limiting.\textsuperscript{158}

The female mite digs burrows in the stratum corneum and granulosum of the epidermis.\textsuperscript{157} In these burrows the female lays 2 to 3 eggs a day which need 2 to 3 days to hatch.\textsuperscript{29, 155} The larva, which has only 6 legs, leaves the burrow and moults passing through an 6 legged nymph stage before becoming adult.\textsuperscript{29, 159} It takes 10 to 14 days for an egg to develop into an adult stage.\textsuperscript{29} The mites feed on the lymph and lysed tissue of their host.\textsuperscript{158}

The survival of scabies mites off the host is limited. During in vitro experiments at room temperature mites were found to survive 24 to 36 hours off the host while keeping their infestive capacity to re-establish on a host.\textsuperscript{160} Mites exposed at 25°C survive for two and three days in an environment at 30% and 90% relative humidity.\textsuperscript{154} Low temperature and high relative humidity favour survival but the capacity to penetrate the epidermis decreases as the mite is longer away from the host.\textsuperscript{155}

It is generally accepted that close physical contact is a common mode of transmission.\textsuperscript{157, 13, 29, 159} There is however much controversy over the role of fomites,
inanimate objects temporarily carrying mites, in the transmission of scabies. Some experts believe that transmission through fomites could even be more important than physical contact\textsuperscript{157} while others believe that this mode is of minor importance.\textsuperscript{154} It cannot be denied that living and infestive mites capable of re-infestation can be present on objects that are in close contact with a scabies patient\textsuperscript{161} but there is no clear evidence that these are also responsible for infestations in humans. Fomites could be important in the transmission of scabies, especially if the patient has a high load of mites, but their exact role remains to be determined.\textsuperscript{162}

The clinical presentation of scabies is pleomorphic.\textsuperscript{159} The typical burrows are a pathognomonic sign. These burrows can be associated with papular, vesicular or erythematous lesions.\textsuperscript{158} A small vesicle can be found where a burrow terminates.\textsuperscript{157} Burrows contain mites, eggs and faeces or scybala. The mite and the burrows are usually found on the finger webs, the wrists, the extensor side of the elbows, on the genitals, buttocks, axillae, waistline and around the nipples. It is not known why the scabies mite favours these locations.\textsuperscript{158} Sometimes multiple urticarial papules develop on the whole body. These lesions do not contain the mite or its products. It is hypothesised that they result from an allergic sensitivity reaction due to cell-mediated or humoral immune responses.\textsuperscript{158} Nodular lesions are also frequently found on the anterior fold of the axillae, the groin, the genitalia and on the buttocks. These nodules can persist for months after a successful treatment.\textsuperscript{155} Usually the head and neck are not involved, and lesions on the chest and back are rare.\textsuperscript{157} Other lesions such as scales, crusts and excoriations are not uncommon (Fig. 8).\textsuperscript{159}

Scabies can mimick other skin diseases. Eczema, allergic reactions, papular urticaria, impetigo, syphilis, dermatitis herpetiformis, viral exanthemas, insect bites, pruritic urticarial papules and plaques of pregnancy, linear Ig A bullous dermatosis and pityriasis rosea need to be taken up in the differential diagnosis.\textsuperscript{155,158,159} The most prominent complaint of scabies patients is itching which can be mild to severe. Often the itching is worse at night. It is not clear if this is because of mite related factors or just because a patient is more aware of pruritus in absence of other stimuli.\textsuperscript{158}
Fig. 8: Clinical lesions of scabies. A) Burrow on the palm of the hand. B) Burrow on the finger web. C) Papules and scratch lesions on the trunk of an adult. D) Erythematous and nodular lesions on penis and scrotum. E) Papules and small burrows on the trunk of an infant. F) Pustules on the palm of an infant.
In a primary infestation it takes 4 to 8 weeks before symptoms start to appear. It is suggested that sensitisation to mite related antigens develops during the incubation period. In a reinfestation the host is already sensitised and the incubation period is much shorter with symptoms developing within 24 to 48 hours.158

Children generally present with the same type of lesions but these can occur in atypical locations, such as the head and neck area. Pustules presenting on the palms may be confused with acropustulosis. Pruritus may interfere with sleeping and eating (Fig. 8E, F).13 The skin reaction to the mite is often less inflammatory in the elderly. Especially in bedridden patients, lesions can be seen on the back which does not usually occur in healthy adults.154

The administration of corticosteroids (topical or systemic) diminishes symptoms and lesions or leads to atypical forms making it difficult to diagnosis scabies. This form is referred to as scabies incognito. Lesions are also difficult to find in persons who frequently bathe, presumably because mites are washed away.

Crusted scabies (formerly known as Norwegian scabies) is caused by the same type of mite that causes classic scabies but is characterised by the presence of thousands or millions of mites.155 Patients with crusted scabies have been reported as the source of outbreaks within institutions for the elderly.163 In crusted scabies, patients present with thick psoriasiform hyperkeratotic lesions on the hands and feet and hyperkeratotic nails. An erythematous scaling eruption can be present on the face, neck, scalp and trunk but burrows are often absent or invisible.13,164 Crusted scabies is not common. It tends to develop in patients with immunodeficiency (HIV, HTLV-1, T-cell leukaemia) or on immunosuppressive therapy (e.g. in organ transplantation). It has also been reported that the application of topical corticosteroids promotes the transformation of classical scabies into crusted scabies. Finally patients with cognitive dysfunction (dementia, Down’s syndrome, mental retardation) or poor cutaneous sensation (syringomyelia, tabes dorsalis, traumatic spinal cord injury) are at risk because they do not feel the itch and/or do not scratch. It has been hypothesised that scratching is some sort of defence mechanism because scratching removes mites and destroys burrows.13,155,159,164 In patients with spinal cord injury scabies may induce increased spasticity in absence of itch.165
An early diagnosis, efficient therapy and identification of persons or groups at risk is of paramount importance in the management of scabies. These topics will be discussed in detail in the next chapters.

The literature used to discuss the topics, was searched in a systematic way in order to find all relevant publications. Different databases were searched, such as PubMed and ISI Web of Science, using MeSH headings such as “Scabies”, “Sarcoptes scabiei” combined with other headings and subheadings such as “Permethrin”, “Ivermectin”, “diagnosis”, “therapy”, “transmission”,… This search was repeated regularly.

Interesting literature that was not indexed was also found in references of some publications.
2. Diagnosis of scabies

As discussed earlier, scabies can be hard to diagnose because of its pleomorphic clinical presentation and because it may resemble a lot of other skin diseases. One of the main issues in the management of scabies is therefore:

What are the key elements for the diagnosis of scabies and what is the value of diagnostic techniques?

The diagnosis of scabies is mainly based on the anamnesis and clinical findings, of which the burrows are pathognomonic. However, patients often present with non-specific symptoms. Scabies may mimick many other dermatologic conditions.

There are only a few diagnostic procedures that might be helpful to establish the diagnosis. The microscopic examination of skin scales is the gold standard. First a drop of oil is applied on a suspect lesion, preferably a burrow, and then the lesion is scraped using a surgical blade. The oil and skin scales are transferred onto a microscopic slide and covered with a cover slip. The specimen is examined under low magnification. The diagnosis is confirmed if a mite, eggs or faeces are found (Fig. 9).

This procedure is very specific, meaning it will not be positive in persons without scabies. However it has a low sensitivity, the mite or its products are found in only 60% of patients in whom scabies is highly suspected. An average scabies patient carries about ten mites. Finding a mite is like looking for a needle in a haystack. Whether or not a mite is found depends on the place were the skin scraping is performed. Therefore a negative skin scraping does not rule out an infestation. Obviously the performance of the skin scraping technique also depends on the skills of the observer.
Another way to collect mites is by a shave biopsy or the “burrow-trucut” technique. A surgical blade or a 2 mm biopsy punch respectively is used to prelevate a burrow.\textsuperscript{170} Non-invasive imaging techniques, such as ELM or dermatoscopy, incident light microscopy and videodermatoscopy have also been described. ELM performed with a dermatoscope with a magnification up to 40 x demonstrated a jet with contrail image corresponding to a mite and its burrow in 93% of the patients in whom scabies was highly suspected.\textsuperscript{166} It has been reported that the typical configuration can also be detected with an ordinary dermatoscope with a magnification of 10 x.\textsuperscript{171}

In incident light microscopy a microscope with a magnification of 200 x is used. A mite was found in all 37 included subjects in whom scabies was suspected.\textsuperscript{172} Videodermatoscopy with a magnification up to 1000 x confirmed scabies in 89% of the scabies patients.\textsuperscript{173} ELM and videodermatoscopy have also been proposed as techniques to monitor treatment (magnification 40 x and 600 x).\textsuperscript{174,175}
These pilot studies indicate that in vivo imaging techniques might be useful and promising tools. However, none of these studies describe the characteristics of the included patients. The spectrum of patients influences the performance of a test because diagnostic tests perform better in patients with a typical presentation. A diagnostic test is only useful if it is able to accurately recognise patients with and without disease, above all in cases where there is great uncertainty about the diagnosis. Furthermore the performance of all the tests mentioned above depends on the skills of the observer.

A test that does not depend on skills, such as a blood test, would be a valuable asset. There are several important obstacles in the development of a diagnostic technique that is based on the detection of antibodies to *S. scabiei var hominis*. A first problem is that mite specific antigens are needed to bind with human antibodies that are directed specifically against the human scabies mite. These antigens are difficult to obtain because human mites cannot be grown in vitro. Animal mites are easier to collect and are therefore used as an alternative. However, tests using animal mites as an antigen source for detection of human antibodies have rather limited results.

One study describing an ELISA using fox mite antigens to detect IgG directed to *S. scabiei* in the serum of human scabies patients had a sensitivity of only 48% and a specificity of 100% in healthy controls and 82% in patients with inflammatory diseases. The antibody titers were higher with increasing severity and duration of disease.

In a second trial with dog mite derived antigens, both IgG and IgE were detected in all patients with crusted scabies but only in a few patients with ordinary scabies. Both studies indicate that the antibody titer most likely depends on the severity of the disease with lower levels of antibodies in mild disease. Diagnostic tests will have a lower sensitivity in mild cases, but it is just in these circumstances that a reliable test is needed.

Another obstacle is a cross-antigenicity between *S. scabiei* and house dust mites. When taking all of the above into account, it does not seem likely that a reliable and useful test will be developed in the near future.
At this time there are no validated diagnostic tests which are useful in the diagnosis of scabies. Furthermore, only skin scraping, the “burrow tru-cut” technique and dermatoscopy can be performed in daily practice. In vivo imaging seems promising but further research is needed to establish its performance in daily practice.
3. Epidemiology of scabies

The two main questions that are relevant to the development of a management of scabies, tailored to our patient population, are:

- What is the incidence of scabies in Belgium?
- What are the risk factors for scabies in Belgian patients?

There is little information on the incidence of scabies because only a few countries, such as Denmark, Poland and Slovenia have a systematic nation wide reporting system. Most studies are based on other sources such as army databases, sentinel practice networks, retrospective research or occasional cross-sectional surveys. These reports can be interesting but it is obvious that conclusions based on surveys in the Israeli army or communities in Brazil, Turkey or Tunis are not applicable to the general patient population that physicians in a Western-European country such as Belgium, have to deal with.

Nevertheless, some patterns consistently return in reports from several countries. During the past century three pandemics have occurred. The first pandemic started around 1915 reached a maximum in 1918 and declined to earlier levels by 1922. A second increase was observed in 1937. This pandemic peaked in 1945 and declined to previous levels by the beginning of the 1950s. A third epidemic began around 1964, peaked in the early seventies and declined towards 1980. The same pattern occurred in several countries in more or less the same time frame which indicates that this pattern is not local.

Recent reports seem to suggest that perhaps a new epidemic has occurred during the last decade of the 20th century. In the UK there has been a sharp increase in the incidence between 1990 and 1995 which continued until 1999. The incidence peaked to 470 cases per 100,000 in 2000 and slowly decreased again. By 2003 the incidence was half the number recorded in 2000. A similar pattern has been observed in Central Poland where the incidence increased continually from 1991 to 1998.
The incidence of scabies shows a variation over time in different countries. Some sources mention that the incidence has a regular pattern with the same cycle occurring every 30 years.\textsuperscript{182,188,189} This regular 30 year cyclic pattern would suggest some periodic changes in the immune status of the population.\textsuperscript{12,182} There are however no arguments to support this hypothesis of herd immunity. A permanent immunity for scabies has not been demonstrated and repeated infestations with scabies are not uncommon. Furthermore there are no such patterns in endemic countries.\textsuperscript{189} Another hypothesis is that some populations act as reservoirs. Fluctuations in the incidence can be caused by population movements such as war or massive tourism.\textsuperscript{189}

Most surveys indicate a seasonal variation with higher incidences during autumn and winter than in spring and summer.\textsuperscript{12,185-189} It is hypothesised that conditions for survival away from the host are more favourable in winter than in summer. Mites survive longer in cold and humid environments, conditions that particularly occur in winter.\textsuperscript{187,189} It has been postulated that cold weather encourages crowding, leading to more favourable circumstances for transmission.\textsuperscript{185}

There is no clear distribution of scabies according to sex or age. In Denmark a higher incidence was observed in girls than in boys from birth up to puberty. The difference disappeared from early adulthood on.\textsuperscript{182} In a survey from Tunisia and in both studies from the UK a higher incidence was found in females.\textsuperscript{185,186,189} In the Polish survey more females than males were affected but the difference was not statistical significant.\textsuperscript{187} No sex difference was found in an endemic area in Brazil.\textsuperscript{187}

It is not possible to make a definite conclusion on a possible sex difference, based on the available literature. A complex analysis of accurate data, taking multiple risk factors into account, is needed but is hard to achieve.

In most reports, scabies is most common in children and young adults and less frequent in the elderly.\textsuperscript{12,187,188} However, one recent report indicated a higher incidence in persons over 75 years, which might indicate a spread of scabies in institutions.\textsuperscript{185}

There has been little research on the influence of socio-economic factors on the incidence of scabies. One study indicated that a greater rate of infestations in rural areas was caused by the lower socio-economic profile of this population. A hampered access to medical services was also suggested as a contributing factor.\textsuperscript{187} In one
report a higher incidence of scabies was found in immigrants versus natives. This 
difference disappeared when only the groups of employed people were compared.\textsuperscript{190}
Scabies has been a notifiable disease in Flanders since 1995. A steep increase has 
been observed starting in 1998 and reaching a peak of 7.5 per 100,000 in 2001 
(Table 2). Since then the incidence has declined again. Further, extensive analysis of 
this database has not been done. The incidence recorded through this system is 
remarkably low, compared to the incidence in other countries.\textsuperscript{185,187} Furthermore, 
40\% and 55\% of the dermatologists and GP’s participating in a survey in Ghent, 
indicated that they rarely or never reported a patient with scabies to the Health 
Inspection. Scabies is probably under diagnosed and under reported, making this 
data unsuitable for the assessment of the magnitude of the problem in the general 
population.\textsuperscript{191}

Table 2: Absolute and relative number of cases of scabies in Flanders reported to the 
Health Inspection services.

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\textsuperscript{1} Absolute number of scabies patients as recorded by the Provinical Health inspection. 
\textsuperscript{2} Total number of inhabitants in Flanders. 
A literature search could not provide a satisfying answer to the two research 
questions mentioned above. Therefore original research was initiated.
In order to assess the incidence of scabies and to identify subpopulations that were particularly at risk, a survey was conducted in 2004 among GP’s (n=344), pediatricians (n=75) and dermatologists (n=32) in Ghent. These physicians were asked to complete and return one form for every new patient diagnosed with scabies. A self-developed questionnaire was used to collect data about demographic characteristics (sex, age, nationality) and patient history (was the patient referred, since when did he have symptoms, had the patient already consulted another physician before). The physician was asked which elements were decisive for the diagnosis of scabies in this patient (contact persons with scabies, nocturnal itch, family members or contacts with itch, scabies burrows, papules, erythema, flakes, crusts, scratch lesions, impetigo). Finally the survey asked which treatment was prescribed and how many contacts of the index patient were treated. Approval for this project was obtained from the Ethics Committee of the Ghent University Hospital (2003/295).

Sixty-nine completed forms were returned, reporting 67 consultations of 64 different persons. One third of all cases were registered by dermatologists at the dermatology department of the University hospital, the rest was filled out by other dermatologists (42%) and GP’s (20%). During the same period, 39 scabies patients were reported to the Health Inspection which is suggestive for an underreporting of scabies through the official channel.

The global incidence of scabies in 2004 in Ghent was 28 per 100,000 inhabitants per year and was the same in men and women. The incidence was almost 4 times higher in immigrants than in persons with a Belgian nationality (P< 0.001, Fisher’s exact test). The highest incidence rates were found in children under 4 years of age (50 per 100,000), in young adults between 15 and 24 (35 per 100,000) and in the elderly (51 per 100,000 in persons over 75) (Fig. 10).

In thirty-six of the 67 consultations (54%), the patient had already consulted a physician for their skin problem. Thirty-six percent of them had received a scabicide treatment and 44% (or 25% of the total group) had received another type of treatment.

Skin scrapings were performed in 64% of the patients and demonstrated mites, eggs or scybala in 70%. Permethrin cream was prescribed for most patients.
There was a remarkable high incidence in persons over 75 which is in contrast to the lower incidence usually found in the elderly. In a recent survey in the UK an increase was also observed in persons over 75 compared to persons between 65 and 74. Older persons frequently require ambulant healthcare and are more often hospitalised or residing in institutions. They have multiple intense contacts with healthcare workers and their fellow residents which poses them at a higher risk of infection. Elderly patients with scabies require extra attention because they often have an atypical presentation and are at a higher risk of developing crusted scabies.

The incidence was almost four times higher in immigrants than in persons with a Belgian nationality. Nationality could be an indicator of SES or living conditions with a non-Belgian nationality reflecting a lower status or worse living conditions. Studies in Poland have shown a higher incidence of scabies in areas with a high level of unemployment and worse sanitary conditions. An Italian study illustrated that not nationality but the associated different SES can be a risk factor for scabies. Another contributing factor could be a language barrier causing difficulties to access health care services.

In 25% of the consultations, patients had already consulted another physician but were not yet treated with a scabicide, which means that either the diagnosis of scabies was not yet established or that the patient was ineffectively treated. This seems contradictory to the results of a survey on knowledge and management of scabies in the same region which showed that the knowledge of GP’s and
dermatologists was of an acceptable level. This will be discussed in Part IV: General discussion & Conclusions.

The results summarised above may be indicative of certain trends but need to be interpreted with care. It is possible that not all cases were registered in this project. Furthermore, these results need to be confirmed by an extensive analysis of a complete data set containing more specific information (such as data on SES, living conditions etc).

The current survey nevertheless suggests that there is still room to improve diagnosis and adequate treatment of scabies. In the management of scabies, extra attention should go out to vulnerable groups, especially migrants, children and the elderly.

A full description of this research is given in Appendix II: Short Report – Incidence of scabies in Belgium. Hilde Lapeere, Jean-Marie Naeyaert, Jozef De Weert, Jan De Maeseneer, Lieve Brochez. Accepted with revisions.
4. Treatment of scabies

Most physicians are aware of the fact that scabies is usually treated with a cream, ointment or lotion. The treatment of classic, uncomplicated scabies is usually not a problem. However, prescribing the correct treatment in specific situations, such as therapy failure, pregnancy, extensive erosions of the skin etc. is more challenging. Therefore a literature search was performed, starting from the following question:

What are the treatment options for scabies, what is their value and place and what evidence is there to support their use?

Scabies can be treated with a number of topical treatments and there is currently also one systemic option available.

The oldest local treatment is sulphur ointment in a concentration between 2% and 10%. This ointment has to be applied over the whole body for three consecutive nights. It is not user-friendly because it is messy, malodorous and stains clothes. It is very cheap and is still used in various countries.\textsuperscript{196-198} DDT in a 6\% alcohol preparation has also been used to treat scabies.\textsuperscript{197} DDT is however banned in many countries since the 1970s because of safety and environmental issues.\textsuperscript{199} Preparations containing balsam of Peru have been marketed in France for the treatment of scabies. The active ingredients are benzyl cinnamic ether and benzyl benzoate. Balsam of Peru is believed to be nefrotoxic when applied over large areas and is notorious for its potential to induce contact allergy.\textsuperscript{196,197} The products mentioned above are not recommended in this time and age because there are few or no studies on their efficacy and more elegant and safer therapies are available.

Products that are currently used worldwide for the treatment of scabies include malathion, lindane, crotamiton, benzyl benzoate and permethrin.

In the UK malathion is suggested as a second-line treatment for scabies.\textsuperscript{200} This organophosphate is well known in the treatment of pediculosis but the evidence for the use of malathion to treat scabies is limited to case series.\textsuperscript{201} Therefore it will not be discussed further.
Lindane is an organochlorine which blocks GABA receptors, which can cause hyperexcitation and convulsions. It is used in a concentration of 1% in cream or lotion. The transdermal absorption of lindane varies between 10% and 90%, depending on the nature of the vehicle. There is some concern about the safety of lindane because there have been reports about central nervous toxicity and deaths, related to overexposure and ingestion of lindane. There is also some evidence about haematological abnormalities. Lindane should not be applied on patients with an altered skin barrier or after a hot bath because this improves absorption. Lindane has been prohibited by law in Belgium since 1997.

Crotamiton is commercially available in Belgium as a 10% cream. In a recent clinical trial good results were obtained with a course of crotamiton once daily for five days. Antipruritic properties have been attributed to this product and it is also claimed to have a low toxic potential.

Benzyl benzoate has been used as an insecticide since the 1940s. In Germany and France it is on the market as a proprietary preparation but in Belgium it is only available as a compounded prescription. Solutions usually contain 25% benzyl benzoate and should be applied for two to three consecutive days. There are only limited pharmacological and toxicological data available. The most common adverse effects of benzyl benzoate are local irritation and contact dermatitis.

Permethrin is a synthetic pyrethroid commonly used for the treatment of pediculosis and scabies. Permethrin 5% cream is only absorbed in small amounts and is completely eliminated after 1 week. The incidence of adverse events associated with permethrin cream is 2.5 per 1,000 of which irritation, burning and stinging are most frequent. An allergic contact dermatitis caused by formaldehyde is rare but occurred in 2 patients per 500,000 treatments. It is regarded to be a safe treatment for pregnant and breastfeeding women and children from the age of 2 months.

Several traditional and two systematic reviews on the treatment of scabies have been published. These have analysed the few randomised controlled clinical trials of good quality that are currently available. A Cochrane review on the subject identified 44 trials and retained 13 trials including a total number of 1747 patients. Because of its low toxic potential and good effectiveness permethrin is the treatment of choice for all scabies patients, including children from 2 months old and pregnant and breastfeeding women. However, the authors of the Cochrane
review on the subject state that the recommendation of permethrin is based on quite small studies together with professional opinion and traditional reviews. It appears that permethrin is more effective than lindane but the studies showed considerable heterogeneity. A cure rate of approximately 90% is reported for permethrin. Two trials including 194 patients studied respectively one and two applications of crotamiton cream. Both treatment regimens resulted in an overall cure rate of 74% and were found to be significantly less effective than one application of permethrin which had an overall cure rate of 94%. In a study from 1999, all participants (n=33) were cured one week after a once daily treatment with crotamiton during five consecutive days.

There is only one study with 158 patients in which 3 consecutive applications with 25% benzylbenzoaat are studied. A cure rate of 91% was found. In another study with only 44 patients a cure rate of only 48% was found for a treatment schedule of 2 applications with a 10% solution.

Ivermectin is the only available systemic treatment option for scabies. It is derived from the avermectines which are produced by *Streptomyces avermitilis*. It binds selectively to glutamate gated chloride ion channels and causes an increased influx of chloride ions with hyperpolarisation of the nerve or muscle resulting in paralysis and death. Ivermectin has a low affinity with mammalian chloride ion channels and does not easily cross the blood-brain barrier making it safe to use in humans. Ivermectin is rapidly absorbed through the intestinal mucosa. A plasma peak occurs about 4 hours after administration, the plasma half life is between 12 and 56 hours. It is metabolised in the liver and excreted in the faeces.

Ivermectin was first used for the treatment of onchocerciasis and has shown to be effective against nematodes, filariasis and larva migrans. No major side effects directly related to ivermectin have been observed. Ivermectin can induce a Mazzotti reactions in patients with systemic parasites. This reaction is characterised by high fever, orthostatic hypotension, bronchospasm and neurologic deterioration. The adverse effects in the treatment of scabies are mild. Increasing pruritus, a skin rash, diarrhoea, vertigo, haematuria, have been observed. There has been one report of an increased mortality in the elderly after the treatment of residents in a ward for highly demented patients. The methodology of this study was flawed and its findings have never been confirmed.
An ivermectin dose of 200 µg/kg body weight has been shown to be effective in the treatment of scabies. \(^{213}\)

The advantages of ivermectin in the treatment of scabies are obvious. This treatment is easy to administer and the whole skin surface is treated at the same time (without any missed spots). \(^{88}\) It can be a valid option for the treatment of patients with generalised eczema, resistance for local treatments or low compliance. \(^{13}\)

Even though ivermectin has some clear advantages, it is not yet clear how it is situated against permethrin. In one clinical trial performed in India, a single dose of 200 µg/kg bodyweight ivermectin was compared to a single application of 5% permethrin cream. Fourty and 45 patients were included respectively in the ivermectin group and in the permethrin group, the family members received the same treatment as the index patient (either ivermectin or permethrin). Significantly more family members were infested in the ivermectin group than in the permethrin group. Fourteen days post treatment, 70% in the ivermectin group and 97.8% in the permethrin group were cured. All non-responders received a second treatment. By the fourth week all patients were cured in the permethrin group and 95% were cured in the ivermectin group. The authors concluded that a single application of permethrin was superior to a single treatment with ivermectin. They hypothesised that one dose of ivermectin might not be effective against the eggs and that a second dose is necessary. \(^{215}\)

However, the higher number of infested family contacts in the ivermectin group might have caused a higher re-infestation and subsequently a lower cure rate in the ivermectin group. Furthermore, the study was performed in India were scabies is endemic, making it difficult to extrapolate the findings to a Western-European population.

A multi-center, randomised, double-blinded, double-dummy study comparing a single dose of 200 µg/kg ivermectin to a single treatment with permethrin 5% cream was started in June 2004 in the University Hospital of Ghent and Antwerp. Patients were eligible if they had scabies burrows or if mites, faeces or eggs were found in the skin scrapings. Patients who had two out of the three minor criteria were also included. Minor criteria were the presence of atypical lesions (papules, vesicles, nodules, excoriations and crusts) with a typical distribution pattern (finger webs, wrists, ...
Part III Scabies | Chapter 4 Treatment

elbows, axillae, around the nipples, on penis scrotum and buttocks), contacts with similar complaints as the index patients and severe itch that worsens at night.

Patients were excluded if they were positive for one of the following criteria: pregnancy, breastfeeding, younger than 5 years, scabicide treatment less than 4 weeks before inclusion, topical corticosteroids less than 1 week before inclusion, HIV positivity, severe immune suppression or allergy for one of the components of the study medication.

A total of 160 patients needed to be included to obtain a power of 0.80 and significance level of 0.05. Every patient received a single treatment consisting of pills and a cream. Some treatments contained placebo pills and permethrin cream. Other treatments contained ivermectin pills and placebo cream. The treatment was allocated at random and both the investigator and the patient were unaware of the composition of the treatment. The cream was applied by the investigator and the pills were taken under supervision.

During the inclusion visit, a thorough anamnesis and physical examination was performed. All skin lesions were counted and recorded and the patient was photographed. Female patients received a pregnancy test. Each patient had to fill out a (Children’s) Dermatology Life Quality Index and an SF-36 (Generic quality of life questionnaire) to evaluate the impact of their skin disease on their daily activities. The itching was quantified using a visual analogue scale.

The patient was evaluated 14 and 28 days post treatment. The primary endpoint was the absence of lesions on day 28. Secondary endpoints were improvement of itch, improvement of quality of life and the number and severity of side effects.

A total of 27 scabies patients were screened. Thirteen actually participated and 14 patients did not meet the inclusion criteria or refused to participate. Two patients dropped out because they applied Zalvor cream on their own initiative and 4 patients were lost to follow up which leaves 7 patients available for evaluation at day 28.

The study was ended prematurely in October 2005 because the recruitment of patients went extremely slow. At the observed rate of inclusion, it would take more than 10 years before enough patients were included. The enrolment of patients was hampered because only one family member was included in the trial and received treatment. Patients also hesitated to participate because they would receive what they felt was an “experimental therapy” and their family contacts had to pay for their own treatment anyway. Patients often did not to stick to the study protocol and
treated themselves with other medication. Finally, the treatment of scabies cannot be postponed to limit the spread of the disease. Therefore the investigator always had to be standby to include patients which is difficult to combine with other activities.

When all the available evidence is taken into account, permethrin 5% cream is the treatment of choice at this time for uncomplicated scabies. Crotamiton applied for five consecutive days can be an alternative, but is less effective. There are few trials of good quality to substantiate the effectiveness of benzyl benzoate. However, in Belgium an emulsion with 25% benzyl benzoate is reimbursed and is much cheaper for the patient than permethrin or crotamiton. Therefore 3 consecutive applications with benzyl benzoate 25 % emulsion might be a good alternative when the financial cost of treatment is an important issue. The compounded prescription for permethrin cream is not reimbursed but is nevertheless cheaper than Zalvor®. Ivermectin seems to be effective in the treatment of scabies but it is not clear if it results in a lower, equal or higher cure rate than permethrin. It can be a good alternative for patients with extensive skin lesions, low compliance or treatment failure.

In crusted scabies, millions of mites are present and the patient is highly infective. This form is often very difficult to treat and frequently relapses. It is treated with the same therapeutic arsenal as ordinary scabies but there are no uniform guidelines on the preferred substances or treatment schedules. Hyperkeratotic crusts need to be removed using 5% or 10% salicylic acid in petrolatum to ensure an optimal penetration of the topical treatment. It is usually necessary to combine several doses of ivermectin with multiple applications of a local scabicide. It is important to trim and extensively treat the nails because these can harbour mites and act as a reservoir. Furthermore, these patients are at high risk of developing bacterial superinfections leading to septicaemia which requires appropriate antibiotic treatment. Because this condition is highly infective the patient needs to be isolated. The patient’s belongings and environment need to be decontaminated carefully.
5. The management of scabies

The management of scabies can be approached from two angels. From a general point of view, the first requirement to practise medicine and manage a disease is the acquisition of adequate knowledge on the subject. This knowledge has to be correct and up-to-date. Some physicians working in the region of Ghent indicated that there was an urgent need for more information about how scabies should be handled. This led to the first research question in this chapter:

Is there a deficit in the knowledge about scabies among GP’s and dermatologists in Belgium?

There is only one study that investigated the knowledge about scabies among general practitioners in Pakistan. A total of 200 GP’s was interviewed using a pre-tested multiple choice type questionnaire on case finding and management of scabies patients. Only 36% of the GP’s had a satisfactory knowledge of scabies, defined as correct responses to 75% of the questions asked.

In order to explore a possible deficit in knowledge on the management of scabies, a survey among GP’s and dermatologists in the region of Ghent was organised during a scientific meeting. To this end, a questionnaire in Dutch was constructed, containing knowledge questions that were categorised into 5 topics involving the biology, incubation period and transmission, diagnosis and treatment of scabies, and crusted scabies. The questions were of the ‘true or false’ and ‘single best response’ type. The Mann-Whitney U test was used for analysis of the differences between GP’s and dermatologists on treatment preferences and hygienic advice. A cumulative logit model was used to examine the effect of three independent variables (profession, number of years of experience and the estimated number of scabies patients per year) on the score obtained on the knowledge test.

Fifty-five GP’s and 82 dermatologists completed the questionnaire, resulting in a participation rate of respectively 86% and 78%. About 40% of the dermatologists and 55% of the GP’s answered that they rarely or never reported a patient with scabies to the Health Inspection. The median score on the knowledge test of all physicians was
29/39 (74%) which is of an acceptable level (Fig. 11). When incorporated in the cumulative logit model, profession, number of years of experience and estimated number of patients all had a statistical significant effect on the score on the knowledge test. The odds of obtaining a higher score are 12.5 times higher in dermatologists than in GP’s. Similarly the odds of obtaining a higher score are 1.51 times higher per increasing category of practice experience and 1.69 times higher per increasing category of the estimated number of scabies patients. Permethrin cream (the current treatment of choice) is prescribed by more than 90% of both dermatologists and GP’s. Finally the hygienic advice given by dermatologists and GP’s was similar. All of the dermatologists and GP’s advised their patients either to wash all their clothes and linen or to keep it in a plastic bag. Thirty-five percent of the GP’s and 9% of the dermatologists advised mopping or disinfecting the bedroom and/or living room (P < 0.001).

This survey was done with a self-constructed questionnaire that was not validated before use. However it was not the intention to develop a universal instrument to test knowledge and practice of scabies but rather to explore the knowledge on the current insights in scabies and to identify a need for education programs in local GP’s and dermatologists. In spite of the fact that the survey was conducted during meetings that are usually attended by a large proportion of the target group, it is possible that we did not reach a representative sample of physicians. The physicians participating in this survey were attending a scientific meeting and knew about the scabies survey. The dermatologists came from a large region in Flanders while the GP’s were all from
the region of Ghent. It is also possible that responders tend to give answers that put them in a positive light, even though the survey was anonymous. These factors could be responsible for an overoptimistic estimation of the knowledge level. Nevertheless, these results can give some idea of the way GP’s and dermatologists in Belgium manage scabies.

A full description of this research is given in paper 5.


In a clinical setting, the correct management of scabies comprises an accurate and early diagnosis, adequate treatment strategies and follow up of treatment. In a literature study of reports on scabies epidemics in institutions, a delay in diagnosis, inadequate treatment and a too short follow up period were identified amongst others as risk factors for the spread and recurrence of scabies in institutions. The main question that a clinician will ask, when dealing with scabies is:

What steps are important when handling a case of scabies?

These steps are extensively discussed in the guideline: “Aanbeveling voor goede medische praktijkvoering: Scabiës”. This guideline is directed towards GP’s and is currently in preparation. It will probably be published by the end of 2007. Some important elements are briefly discussed below.

As discussed in Chapter 2, the diagnosis of scabies is mainly based on anamnthesis and clinical findings. Therefore it is important that physicians are capable of identifying suggestive elements in the patient’s history. Furthermore, they should be able to recognise the pathognomonic features of the disease, as well as the whole range of atypical lesions. A skin scraping is an easy and fast procedure to confirm the
diagnosis. It enables the physician to be 100% sure of the diagnosis, at least in the case of a positive test result.\textsuperscript{13}

When prescribing a treatment for scabies, a physician should combine the best available research evidence with his/her clinical expertise and the patient’s values and circumstances.\textsuperscript{19} The current best evidence indicates that permethrin 5\% cream should be preferred as the first-line treatment.\textsuperscript{206} However, it might not always be the best choice, for instance if the patient has extensive dermatitis or is on a very tight budget.

Next in importance to treating the index patient, is to simultaneously treat all contacts, whether they have symptoms or not. Because of the fairly long incubation period, contacts may already be infested without having any lesions or symptoms. Patients should also receive advice about the environmental measures, even if there are no hard data to prove that these measures actually reduce transmission. It is sensible to wash all clothing and linen that has been in contact with the skin for the past three days at a high temperature (60\textdegree). Material that cannot be washed should be isolated in a plastic bag for three days.\textsuperscript{13}

It is advisable to regularly evaluate the patient in order to detect treatment failure in an early phase. Treatment failure can occur if there is poor compliance or if the patient does not meticulously follow the given instructions. A relapse or reinfection can also be a cause of treatment failure. In such cases the whole treatment procedure (including treatment of contacts) should be repeated. Finally, there is also the possibility that the mite has developed resistance to the administered treatment.\textsuperscript{13} Resistance is difficult to diagnose because an active infestation is hard to distinguish from residual lesions or reinfection. It is also difficult to perform in vitro resistance tests because a lot of mites are needed. Scab mites cannot be cultured in a lab and need to be collected from patients with crusted scabies.

Resistance to lindane and crotamiton has been reported in the past.\textsuperscript{218} Recently resistance to ivermectin has been observed in vivo and vitro in scabies mites from two patients with crusted scabies that received respectively 30 and 58 doses of ivermectin during the past 4 to 5 years. This observation demonstrates that scab mites are able to develop resistance to ivermectin after intensive use of the product.\textsuperscript{219}
As far as permethrin is concerned, an increased tolerance has been demonstrated in vitro. However until today, resistance to permethrin has not been documented in vivo.\textsuperscript{220}

At this time there is little evidence that resistance to scabicide treatments is a major clinical problem. However it has been demonstrated that scab mites can develop resistance and this might become more important in the future. Resistance should be taken into account if a patient was treated correct and if there is no evidence of reinfestation. In those cases another type of active molecule should be used (e.g. switch from permethrin to ivermectin).

The follow-up of a scabies treatment is very difficult because the itch disappears very slowly and because some lesions, such as nodules, may be present for a long time, even after a successful treatment.\textsuperscript{13,14,159} If the patient is evaluated too soon, it will be difficult to assess progression. If the patient is evaluated too late, a treatment failure might be discovered too late, leading to a further spread of scabies. There are no clear guidelines in the literature on when the treatment should be evaluated. However, in clinical trials, patients are usually evaluated after 14 and 28 days. If the itch and/or lesions are not better, the patient is treated again.\textsuperscript{206} It is not advisable to perform a skin scraping before 14 days because the skin needs some time to slough off dead mites and other debris. It seems reasonable and feasible to adopt this scheme into daily practice.\textsuperscript{159}

Scabies is becoming more and more a problem in institutions.\textsuperscript{185} A case of crusted scabies has often been the source of epidemics in institution.\textsuperscript{221} The management of institutional outbreaks requires a lot of work and effort of all persons concerned. Central issues in the management of scabies in institutions are the optimisation of case detection, the distribution of (written) information, the coordination of treatment and hygienic measures, adequate follow up and the implementation of preventive measures such as an increased awareness and education of all personnel. Institutions should develop a strategy which starts as soon as one patient develops a rash which raises suspicions of scabies.\textsuperscript{14,222}
Part IV General discussion
& Conclusions
General discussion & conclusions

Pediculosis capitis and scabies are very common skin infestations. Nevertheless, there is a great need for epidemiologic, diagnostic and therapeutic studies of good quality on which management of both diseases can be based. It is also remarkable that there is a lot of controversy about the methodology used in both fields. Authors disagree on the diagnostic criteria and procedures that should be applied, the methodology for epidemiologic research and the criteria to evaluate treatment options.103

First, the main aspects in the management of pediculosis will be discussed, followed by a discussion of the important elements in the management of scabies. To conclude, an agenda with suggestions for future research is given.

It seems obvious that pediculosis is diagnosed when a living, moving louse is found.47 However, in many scientific studies no discrimination is made between the presence of eggshells, which is a sign of a past infestation, and the presence of living lice.53,61-63,65

A second issue, troubling the diagnosis of pediculosis, is the lack of a gold standard for the detection of head lice.47 As discussed in Chapter 2 of Part II, a multitude of detection methods have been described but only three of them, VI, DC and WC, have been tested for their accuracy. Studies show that the diagnostic accuracy of visual inspection is inferior to the accuracy of the other two methods. However, there were no data on how dry combing and wet combing relate to each other.

The accuracy of visual inspection, dry combing and wet combing has been studied in a population of schoolchildren by screening all children with the three methods on the same day. (Paper 1) The sensitivity of wet combing was almost 2.5 and 1.25 times higher than the sensitivity of respectively visual inspection and dry combing. The sensitivity of dry combing was about 2 times higher than of visual inspection. Wet combing was the most accurate method but did not prove to be watertight because 11% of the cases were missed. The economic evaluation showed that wet combing is more expensive and time consuming than dry combing or visual inspection.
When choosing a diagnostic method, the setting of the screening needs to be kept in mind. If a large number of children need to be screened, it could be useful to resort to dry combing if the appropriate conditions (or funding) for wet combing are not available. However, it has already been demonstrated that it is feasible to perform wet combing in a large groups of children. Wet combing is certainly the method of choice for the screening of children at home because water and conditioner are readily available.

More than 20 reports on the prevalence of pediculosis have been published over the last decade. There is however much uncertainty about the role of potential risk factors such as personal characteristics of the child, crowding and socio-economic status. The discrepancy in the results of the prevalence surveys can partly be explained by the different diagnostic criteria, diagnostic methods and statistical methods used. (Chapter 3 of Part II)

A large pediculosis screening on 6169 children has been performed in 2001 in Ghent, to measure the prevalence of pediculosis in the region but also to explore the role of different possible risk factors. (Paper 2)

Live lice were found in 8.9% of the children and another 4.6% had nits without lice. A multi-level analysis showed that the child’s class and school had a greater impact on the risk of getting head lice than his or her individual characteristics. SES, the number of children in the family, the length of the child’s hair and hair colour were the only significant factors on the individual level.

These results should be interpreted with care because there is not necessarily a causal relationship between the mentioned risk factors and the prevalence of lice. The risk factors probably lead to a higher prevalence because they hamper diagnosis or treatment.

The treatment of pediculosis has been discussed in Chapter 4 of Part II. For several reasons it is impossible to give unequivocal advice on the treatment of pediculosis at this time. There is a lack of randomised controlled trials with products to treat head lice. There is currently neither a gold standard to detect head lice nor a consensus on how and when a pediculicide should be evaluated. There is also controversy on when a second treatment should be applied. It is suggested that treatment should be
repeated 10 days after the initial application because it can take up to 10 days before the eggs hatch.28

There is also a lot of discussion on the criteria that should be used to evaluate clinical trials.104,105 The fact that two systematic reviews came to conflicting results, based on the same clinical trials, illustrates the complicated situation. (Appendix I)

Furthermore, we need knowledge about local resistance patterns in order to advise appropriate, effective pediculicides. Reliable, fast and cheap detection methods are needed for the repeated epidemiological assessment of local resistance patterns, based on bio-assays and if possible, on genetic screening for mutations in head lice.

New substances, such as essential oils, have become very popular of the last years. Some of them have also shown good in vitro pediculicidal activity. However, clinical trials are needed before these products can be advised to the general public.

The lack of trials is even more obvious in the removal of eggshells because there was only one, biased clinical trial that studied the effectiveness of a nit removal system103,133, which is discussed in Chapter 4 of Part II. Because no objective measurement procedure was described in the literature, we developed an affordable, feasible and reliable method to measure the force needed to remove nits from the human hair. (Paper 3) The method was slightly modified to facilitate data handling.

The improved measuring procedure was used to test the effect of several products on the forces needed to remove nits from the human hair. (Paper 4) From these in vitro tests we can conclude that a short application of conditioners significantly reduces the force needed to remove nits. The continuous application of conditioner results in a further reduction of forces compared to a short application of the same product. We could not demonstrate any difference in efficacy between an ordinary conditioner and specific nit removal products. Furthermore, solutions with FA did not have an additional effect when compared to pure deionised water.

This research suggests that the continuous application of an ordinary conditioner significantly enhances nit removal. The clinical relevance of this finding needs to be confirmed by in vivo tests.

Finally, in order to manage pediculosis, a policy should be developed that involves the whole community. The role of parents, teachers, school nurses, school administrators, pharmacists, physicians, local authorities as well as central government has been discussed in Chapter 5 of Part II. The detection and treatment
of pediculosis is mainly a responsibility of the parents. School nurses, teachers, pharmacists and physicians however also play important roles. They should be well informed and support the parents in a non-judgmental way. The government on the other hand should also take up their responsibility by spreading accurate information through the appropriate channels. Furthermore, they also play an important role in the regulations concerning the production, sale, labelling and evaluation of products that claim to kill head lice.

Scabies is caused by *S. scabiei*, a tiny mite barely visible to the naked eye. The diagnosis of scabies is mainly based on the patient’s history and lesions. (Part III, Chapter 2) The gold standard for the diagnosis of scabies is the microscopic examination of skin scrapings. The diagnosis is confirmed if a mite, ova or scybala are seen.\(^{154,166}\) This diagnostic technique is however often negative and there is a need for more accurate diagnostic procedures. Imaging techniques have been shown to be useful but these may also depend of the skills of the observer or are to expensive to be used in routine practice.\(^ {172,173}\) In vivo imaging seems promising but more research is needed to demonstrate the performance of these techniques in the diagnosis of scabies. Laboratory tests on the serum of the patient are not sensitive enough yet to be of clinical importance.\(^ {177}\)

The difficulty to establish the diagnosis of scabies might be one of the reasons why there are little reports on the prevalence or incidence of scabies. (Part III, Chapter 3) Another reason for the paucity on epidemiologic data on scabies could be the fact that only a few countries have a nation wide reporting system.\(^ {181-183}\) The studies that are available are frequently based on army databases, sentinel practice networks or patient charts.\(^ {185,186,223}\) These studies are often not representative for the population that physicians in Belgium have to deal with.

A prospective survey of the incidence of scabies in Ghent was organised in 2004. All GP’s, dermatologists and paediatricians in this region were asked to report every new scabies patient they encountered during that year. (Appendix II)

The age distribution of the encountered scabies patients showed a remarkable peak in persons over 65 which is in contrast to the usual age distribution of scabies. This could be indicative of a growing number of scabies infestations in institutionalised persons. A four times higher incidence of scabies was found in persons of non-
Belgian nationality than in persons of Belgian nationality. It is hypothesised that nationality is rather an indicator of SES with immigrants having a lower SES. Similar results have been found in an Italian study. They found that nationality did not play a role anymore when only the subset of employed patients was evaluated. Another factor contributing to a higher incidence could be a language barrier, causing delayed access to health care and thus further spread in this group.

Slightly more than half of the patients reported in our survey had already consulted a physician before. In 44% of these cases (which is about one quarter of the reported cases), the patient hadn't received a scabicide treatment. This may indicate that the diagnosis was not established yet or that an inappropriate treatment had been prescribed.

These results may be indicative of certain trends but need to be interpreted with care. It is possible that not all cases were registered in this project. Furthermore, these results need to be confirmed by an extensive analysis of a complete data set containing more specific information (such as data on SES, living conditions etc).

The treatment of scabies has been discussed in Chapter 4 of Part III. As in pediculosis, the evidence on which treatment advice should be based is rather flimsy. Again, the lack of a gold standard significantly hampers the methodology of clinical trials. Furthermore, the infectious nature of the disease makes it difficult to control for reinfestation. As a result, the number of clinical trials of good quality is limited. A systematic review stated that permethrin is the treatment of choice but that “this choice is based on small studies together with professional opinion and traditional reviews”.

This review also stated that crotamiton is less efficacious than permethrin cream. For benzyl benzoate there is currently not enough information available about its effectiveness because there are no clinical trials of good quality comparing it to permethrin or crotamiton. However, it can still play a role in the treatment of scabies because it is very cheap. It could be a good option when the cost of the treatment is an important issue for the patient.

Recent trials have demonstrated the scabicide properties of ivermectin tablets. It is not quite clear yet what the exact role of ivermectin is in the treatment of scabies, because only one study compared this product with the current standard treatment, permethrin. This study was performed in an endemic area which is not representative
for our Western-European population. Furthermore, a higher number of contacts were infested in one of the treatment groups which could explain the observed differences.

A double-blind, double-dummy, placebo controlled clinical trial comparing 5% permethrin cream to a single dose of ivermectin tablets at 200 µg/kg body weight was started in 2004 but ended premature in 2005. From this study, several pitfalls could be identified. Next to the earlier discussed difficulties in establishing a diagnosis, the relatively low incidence of scabies in Belgium also proved to be an important obstacle. Furthermore, it was difficult to persuade patients to participate in a study in which only one treatment was for free and the other contacts had to pay the treatment themselves. The compliance of patients to stick to the study protocol was often poor. Because of the infectious nature of scabies, it is best to treat scabies immediately to limit the spread of the disease. Therefore, the investigator always had to be stand-by to include patients.

Finally, several aspects of the management of scabies are discussed in Chapter 5 of Part III. A guideline about the management of scabies is currently under development will be published by the end 2007.

From a general point of view, sufficient knowledge about a disease is a prerequisite for the adequate management of this disorder. A survey on the knowledge and management of scabies in GP’s and dermatologists was organised to explore whether there was a need for more education and information about the topic. (Paper 5) The knowledge level of both groups was of an acceptable level. The number of years of experience, profession and estimated number of patients influenced the score on the knowledge test. Physicians with more experience and physicians who estimated to see more scabies patients had a better test result. Dermatologists scored better than GP’s. This seems to indicate that the knowledge about scabies increases with increasing experience with this disease.

The relative good results on the knowledge test seem to be in contradiction with the results of the epidemiologic study that was described earlier. In the latter, it was observed that almost one quarter of the patients had to consult a physician more than once before scabies was diagnosed or treated in a correct way. The results of the epidemiologic study are however rather an addition to the knowledge survey than a contradiction. It gives a realistic idea of what is happening in daily practice as
opposed to a knowledge survey that explores the “passive” knowledge. It is possible that we did not reach a representative sample of physicians in the knowledge survey, in spite of the fact that the survey was conducted during meetings that are usually attended by a large proportion of the target group. There could have been an inclusion bias, resulting in an overoptimistic estimation of the knowledge level. On the other hand, it is also possible that the passive knowledge about scabies is sufficient but that physicians have difficulties to translate their knowledge into practice.

Some elements in the management of scabies and pediculosis need to be researched in the future. The first and maybe most important element is the diagnosis of both pediculosis and scabies. It has been demonstrated that the sensitivity of wet combing is superior to the sensitivity of two other frequently used methods. Nevertheless, information about the specificity of this method is currently lacking. The diagnosis of scabies is probably even more challenging. A great step forward would be the development of an accurate, objective diagnostic method. Some epidemiologic aspects also deserve further clarification, especially in scabies because unequivocal data are lacking. The recognition of risk factors for scabies could however help to develop a policy for disease. It is important that epidemiologic surveys are also performed in populations that are representative for the population in a Western-European country. There is currently a lot of controversy about the treatment of both pediculosis and scabies. In the case of pediculosis there is an urgent need to establish a set of criteria that good clinical trials have to meet. Furthermore, the resistance to pediculicides needs to be monitored in order to adjust treatment advice. In the case of scabies there is a need for clinical trials comparing substances such as benzyl benzoate or ivermectin to the current standard therapy.

The suggestions for further research seem quite long. This list has to be tackled item by item. During the Third International Congress on Phthiraptera from 16th – 20th October 2006, a round table discussion on the quality criteria for clinical trials of treatments of head lice was organised. Items such as inclusion criteria, type of intervention (single versus double treatment), methods to assess cure rate etc. were
discussed. A consensus was not yet reached because some aspects needed further study. However, the participants agreed to continue the discussion via e-mail.

During the past two centuries, the development of medicine has been characterised by a continuing struggle between experimental physiology and clinical epidemiology. However, history has shown that none of both methodologic genres is superior to another but rather that they are complementary. In an attempt to provide new evidence that is founded on a broad scientific basis, research in both domains performed and combined in this thesis.
Part V References
Part V: References

References


119. Instructions for determining the susceptibility or resistance of body lice and head lice to insecticides. *WHO/VBC/81.808* 1981.


