

Epidemiology of molluscum contagiosum in children

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This thesis is being submitted in partial fulfilment of
the requirements for the degree of
Doctor of Philosophy

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Summary

Molluscum contagiosum (MC) is a common skin condition in children presenting to primary care in the United Kingdom (UK) and is typically diagnosed based on its distinct appearance. There are limited data on the epidemiology of MC in UK children. Little is known about its presenting symptoms, time to resolution, likelihood of transmission and impact on quality of life (QoL), highlighted within a systematic review of the epidemiology of childhood MC presented early in this thesis. This thesis aimed to address this gap in evidence.

A retrospective longitudinal cohort of 9,245,847 children registered at primary care centres in the UK extracted routinely collected data from the Clinical Practice Research Datalink (CPRD). The study highlighted decreasing trends in consultation rates for MC by 50% during the 10 year study period 2004-13. Children who were previously diagnosed with atopic eczema were more likely to have a future MC consultation than controls.

The 'Molluscum Contagiosum Diagnostic Tool for Parents' (MCDTP) was developed to aid parents in diagnosing spots, lumps or bumps on a child's skin as being MC or not. The MCDTP was assessed in primary care centres to measure its diagnostic accuracy (n=203, sensitivity=92%, specificity=88%), and used to recruit a prospective community cohort of 306 UK children with MC. Results showed that MC lesions were most common on legs and arms, and nearly 70% of children had lesions in more than one site. The average time to resolution was 12 months, however over a quarter still had lesions after 18 months and 12% after 24 months. Nearly half of households reported transmission to one or more children from an index case. Overall MC had a small effect on QoL however, 1 in 10 children experienced a very severe effect on QoL.

The findings presented in this thesis can facilitate self-care of MC in the community where parents can self-diagnose their child's spot, lumps or bumps on the skin as MC or not using the MCDTP. These data can provide parents, and other interested stakeholders, with accurate information of the epidemiology of the condition to aid the management in both clinical and community settings.

Abbreviations

AA	Alex Anstey (Dermatologist)	MHRA	Medicines and healthcare products regulatory agency
AE	Atopic eczema	MOSAIC	Molluscum contagiosum in the community
AI/AN	American Indian / Alaskan Native	NF	Nick Francis (Academic supervisor, GP)
AYF	Andrew Finlay (Dermatologist)	NHS	National health service
BNF	British national formulary	NICE	National institute for health and care excellence
CDLQI	Children's dermatology life quality index	NISCHR	National institute for social care and health research
CI	Confidence interval	NPV	Negative predictive value
CPRD	Clinical practice research datalink	NRES	National research ethics service
CRC	Clinical research centre	ONS	Office for national statistics
DLQI	Dermatology life quality index	OR	Odds ratio
GP	General Practitioner	PIC	Participant information centre
HIV	Human immunodeficiency virus	PPV	Positive predictive value
ICD-10	International classification of diseases (v10)	PR	Public relations
ID	Identifier	PRISMA	Preference reporting items for systematic reviews and meta-analysis
IMD	Indices of multiple deprivation	PST	Psoriasis screening tool
ISAC	Independent scientific research committee	QoL	Quality of life
JG	John Gallacher (Academic supervisor, Epidemiologist)	RR	Relative risk
JO	Jonathan Olsen (PhD Candidate)	SW	Samantha Woods (Lay representative)
JSA	Job seekers allowance	UCI	Upper confidence interval
LCI	Lower confidence interval	UHB	University health board
LSOA	Lower super output area	UHW	University hospital of wales, Cardiff
MC	Molluscum contagiosum	UK	United Kingdom
MCDTP	Molluscum contagiosum diagnostic tool for parents	UKCRN	UK clinical research network
MCV	Molluscum contagiosum virus	VP	Vincent Piguet (Academic supervisor, Dermatologist)
MeSH	Medical subject heading	WSPCR	Wales school for primary care research

Table of contents

Chapter one: Introduction	1
1. Overview	1
1.1 Molluscum contagiosum (MC)	1
1.2 Is there a gap in the knowledge in the description of the epidemiology of MC?	4
1.3 Why is describing the epidemiology of MC important?	6
1.4 Summary	6
1.5 Thesis Aims and Objectives	7
1.6 Patient representation	8
1.1 The MOSAIC study	9
1.2 Approvals, governance, funding and study reporting	9
1.3 Thesis synopsis	11
Chapter two: Systematic review of epidemiological studies of childhood molluscum contagiosum	13
2. Overview	13
2.1 Design	13
2.2 Search Strategy	14
2.3 How prevalent is MC?	15
2.4 What is the Incidence of MC?	19
2.5 Presentation and prognosis of symptoms	23
2.6 What are the reported risk factors of MC?	26
2.7 Discussion	29
2.8 Limitations of systematic review	30
2.9 Conclusions	32
Chapter three: Systematic review of common skin conditions using the children's dermatology life quality index (CDLQI).	34
3. Overview	34
3.1 Children's Dermatology Life Quality Index (CDLQI)	34
3.2 Literature search methods	35
3.3 Results	37
3.4 Discussion	42
3.5 Conclusions	43
Chapter four: Descriptive epidemiology of molluscum contagiosum: longitudinal retrospective cohort of children presenting to primary care in the UK	44
4. Overview	44

4.1	Background	44
4.2	Clinical Practice Research Datalink (CPRD)	45
4.3	Aims and objectives	46
4.4	Study Design.....	47
4.5	Statistical Analysis.....	48
4.6	Approvals	52
4.7	Data extraction and cleaning	52
4.8	Results.....	54
4.9	Discussion.....	65
4.10	Limitations.....	67
4.11	Conclusions	69
Chapter five: Development of a parental molluscum contagiosum diagnostic tool (MCDTP)...		70
5.	Overview	70
5.1	Theoretical Perspective.....	70
5.2	Development of a draft diagnostic tool.....	73
5.3	Approvals and Consent	74
5.4	Phase one: Establishing key features of MC	75
5.5	Phase two: Improving usability of MCDTP.....	79
5.6	Phase three: pilot of MCDTP.....	84
5.7	Discussion.....	88
5.8	Conclusions	92
Chapter six: Assessing the extent to which the MCDTP is valid as a parental molluscum contagiosum diagnostic tool.....		93
6.	Overview	93
6.1	Objectives.....	93
6.2	Study design.....	94
6.3	Inter-rater agreement.....	99
6.4	Recruitment	100
6.5	Sample size.....	101
6.6	Data collection	101
6.7	Practice Retention.....	102
6.8	Data management	102
6.9	Analysis	103
6.10	Results.....	103
6.11	Discussion.....	109
6.12	Conclusions	114
Chapter seven: Prospective cohort study of children with molluscum contagiosum		115
7.	Overview	115

7.1	Background	115
7.2	Study Design.....	115
7.3	Rational for study design	115
7.4	Objectives.....	117
7.5	Population.....	118
7.6	Recruitment processes.....	118
7.7	Procedure.....	125
7.8	Data management	128
7.9	Outcomes.....	129
7.10	Results.....	131
7.11	Quality of Life	140
7.12	Discussion.....	143
7.13	Limitations.....	145
7.14	Conclusions	148
	Chapter eight: Discussion	149
8.	Overview	149
8.1	Main findings	149
8.2	Strengths and weaknesses of key findings	150
8.3	Interpretation of findings and comparison with other published work	155
8.4	Lay representation	160
8.5	Implications and further research	161
8.6	Conclusions	166
	References	167
	Appendices.....	177
	Appendix 1 – Published Manuscripts.....	179
	Appendix 2 – Appendices relating to systematic review	202
	Appendix 3 – Appendices relating to MCDTP development and validation.....	203
	Appendix 4 – Appendices relating to prospective cohort	223
	Appendix 5 – Ethical and research governance approval documentation	235

List of figures

Figure 1. Example of MOSAIC study documents using the study logo	9
Figure 2. GANTT chart of individual studies within this thesis completed during study period.	12
Figure 3. Flow chart of study selection process.....	15
Figure 4. Comparison of prevalence of childhood MC reported in cross-sectional surveys by study subset.....	18
Figure 5. Flow chart of study selection process.....	37
Figure 6. Comparison of mean CDLQI scores by skin condition	41
Figure 7. Case-cohort study sample size calculation	49
Figure 8. Data cleaning and preparation for analysis (MC consultations 2003-14).....	53
Figure 9. Data cleaning and preparation for analysis (MC and AE consultations 2003-14)	54
Figure 10. Consultation rate per 1,000 registered population, 2004-13, by age (year) and gender	56
Figure 11. Consultation rate per 1,000 registered population aged 0 to 14 years, by year and gender.....	57
Figure 12. Consultation rate per 1,000 registered population, males and females, by year and age group	58
Figure 13. Consultation rate per 1,000 registered population, males and females, by quarter 2004-13	62
Figure 14. Correlogram of consultation rates for MC in relationship to point zero by quarter 2004-13	62
Figure 15. MCDTP development process.....	74
Figure 16. Key categories and text for diagnosing MC by Themes.....	79
Figure 17. First draft MCDTP.....	83
Figure 18. Pilot with parent network group (study steps)	85
Figure 19. MCDTP study process in GP practices.....	99
Figure 20. Participant recruitment in GP practices by month	104
Figure 21. Characteristics of sample, English, Welsh and Cardiff populations.....	114
Figure 22. Examples of recruitment and study awareness methods	119
Figure 23. Text message and email follow-up procedure.....	127
Figure 24. Monthly recruitment of study participants	132
Figure 25. Source of recruitment for study participants	132
Figure 26. Number of lesions present by participant at point of survey completion.....	134
Figure 27. Number of anatomical sites MC lesions present	134
Figure 28. Distribution of lesions by anatomical site and frequency of presentation in study participants	134
Figure 29. Advice received from GP (when participant saw doctor)	136
Figure 30. Kaplan-Meier survival estimates of lesions (in months) by gender.....	139
Figure 31. Distribution of CDLQI scores	140
Figure 32. Participants completing CDLQI by severity score band	142
Figure 33. CDLQI meta-analysis including results from this study.....	143

List of tables

Table 1. Prevalence studies of MC (worldwide)	16
Table 2. Incidence of MC.....	20
Table 3. Characteristics of children and natural history of MC	25
Table 4. Association between swimming and MC	26
Table 5. Interpretation of CDLQI score by severity banding (70)	35
Table 6. CDLQI scores of common skin conditions by study, setting and design	38
Table 7. Treatments for AE and severity.....	50
Table 8. MC and AE CPRD Read-codes.....	51
Table 9. Count and percentage of MC consultations aged 0 to 14 years, 2004-13 by Read-code.	55
Table 10. Count and percentage of patient gender aged 0 to 14 years, 2004-13	55
Table 11. Consultation rate per 1,000 registered population 2004-13 aged 0 to 14 years by gender	55
Table 12. Consultation rate per 1,000 registered population,2004-13,by age(year) and gender	56
Table 13. Consultation rate per 1,000 registered population aged 0 to 14 years, by year and gender	57
Table 14. Number of consultations per patient during period 2004-13.....	58
Table 15. Time between initial MC consultation and final consultation between 2004-13.....	59
Table 16. Referral's to secondary care dermatologist per 1,000 MC consultations, males and females, 2004-13, by age group.....	59
Table 17. Referral's to secondary care dermatologist per 1,000 MC consultations aged 0 to 14 years, males and females, by year	60
Table 18. Referrals to dermatology and single or multiple consultations for MC.....	60
Table 19. Treatment prescribed during a patient's consultation for MC	60
Table 20. Treatments coded for diagnosis of MC (where prescribed in over 1% of cases).....	61
Table 21. Number of consultations for AE per patient during period 2004-13	63
Table 22. Time between AE and MC consultation in cases of AE who also consulted for MC...	64
Table 23. Odds ratio (OR) of MC consultation in patients with previous AE diagnosis	64
Table 24. Unadjusted odds ratios (OR) for future MC consultation in children with AE.....	65
Table 25. Recommended wording for use in MCDTP	82
Table 26. Feedback questionnaire to MCDTP	86
Table 27. MCDTP disease definition framework.....	89
Table 28. Participants recruited by practice site	105
Table 29. Participant characteristics.....	105
Table 30. Agreement of MC diagnosis between GP and parent listed by parental diagnostic confidence.....	106
Table 31. Incidence of MC, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for MCDTP	107
Table 32. Inter-rater agreement between reference standard, GP and 2 dermatologists	108
Table 33. Inter-rater agreement between reference standard, GP and 2 dermatologists where suspect and confirmed diagnosis is merged.....	109
Table 34. Social media tools and relevance to health professionals or researchers.....	121
Table 35. Search terms for Google 'Adwords'	123
Table 36. Recruitment timetable by different methods.....	124
Table 37. Participant characteristics.....	133
Table 38. Treatment & Advice	135
Table 39. Association with other conditions.....	137

Table 40. Sporting activities	137
Table 41. Time to resolution of MC lesions	138
Table 42. Association between total duration of symptoms and gender, prescribed and non-prescribed medications, and number of lesions (Hazard Ratio).....	139
Table 43. CDLQI scores at recruitment	141
Table 44. Interpretation of CDLQI score by severity banding (70)	141
Table 45. CDLQI score by domain	142

Chapter one: Introduction

1. Overview

This thesis aims to describe the basic epidemiology, including presenting symptoms, and time to resolution, of the skin condition molluscum contagiosum (MC) in children. Within this initial chapter I will provide a background description of MC in terms of clinical description, virology, histology, treatment, the main risk groups, and research gaps. I will conclude by highlighting why the research conducted within this thesis is important. I will also discuss the importance of describing the epidemiology of common skin conditions.

The specific aims and objectives will be presented at the end of this chapter as well as ethical and research governance approvals.

1.1 Molluscum contagiosum (MC)

1.1.1 Clinical Features

MC is a common skin condition that can present in persons of all ages and is an infection of the skin and mucous membranes (1-3). MC is characterised by discrete, single or multiple flesh coloured papules. MC typically presents as one or more umbilicated, smooth, flesh-coloured, pearlescent, domed shaped lesions (4). Lesions can appear anywhere on the body (5), forming from slightly raised lesions of rubbery consistency up to 5mm in diameter (1). Although lesions are generally self-limiting, for some they can be extensive, cause itching, discomfort, anxiety and social stigma, can result in scarring, and on some occasions bacterial superinfections with inflammation and pain (4, 6).

1.1.2 Virology

MC is caused by a viral infection of the skin and is a member of the poxvirus family which, since the eradication of smallpox, is the most prominent poxvirus presenting in a human host

(7). The MC virus (MCV) is a large double stranded DNA virus (8) which has four major viral types based upon DNA analysis: MCV₋₁, MCV_{-1A}, MCV₋₂ and MCV₋₃. The strand with the highest prevalence is MCV₋₁, which is more common in children, whereas MCV₋₂ affects older people as it is more commonly seen through sexual transmission (9) and is not usually found in patients aged under 15 years (10). MC is a cytoplasmically replacing virus, and the maturation of the virus takes five days (7). Lesions resolve spontaneously, possibly when the virus-infected tissues are exposed to the immune system (4), and the time to resolution of symptoms has not been well described in the literature.

1.1.3 Histology

The lesions are histologically characterised by inverted lobules of hyperplastic, acanthotic, squamous epithelium, which form a central crater that is filled with semiliquid debris (4, 7). The lesions are limited to the epidermal layer of the skin, and have a resemblance to hair follicles (4).

1.1.4 Transmission

Transmission of MC is described as occurring by two routes; direct skin to skin contact (9) or by indirect contact of the mollusca through sharing of towels, bath sponges, clothing or bedding (2, 11). Early studies published in the 1950's described poor hygiene with increasing the likelihood of transmission of MC (12), however this research did not provide statistical associations and since this studies have shown a high proportion of cases of MC in families with average to excellent hygienic standards (13).

1.1.5 Diagnosis

MC is typically diagnosed through clinical examination of the distinct lesions, and are commonly diagnosed and managed in primary care. Unusual and more severe cases may be referred to a dermatologist (2). The condition can be diagnosed by the histopathology found in biopsies of lesions (3), however this is generally uncommon practice in the UK.

1.1.6 Treatment

There are four main treatment options; application of topical agents that cause skin disruption, physical procedures to debride the lesion, systemic treatments such as immunomodulatory agents, or awaiting natural resolution (2, 4, 14, 15). Physical treatment options can be painful and leave the risk of scarring (1). However, it can be difficult to ascertain whether scars result from the treatment or the lesions (4, 16).

Some researchers have recommended that MC should be treated, arguing that in light of the availability of safe, efficacious and convenient treatment options, physicians have the appropriate tools to improve patient quality of life (QoL) while providing a convenient, well-tolerated easily administered treatment regime (6). However, a recent systematic review of cutaneous MC ('a review of interventions for cutaneous MC in non-immunocompromised children and adults') conducted by the Cochrane Collaboration in 2009 found insufficient evidence to recommend any treatment. The review suggested that until there is better evidence for superiority of other treatments then MC should be left to heal naturally (17). 11 studies were included within this review, nine were of topical ointments, one of a systemic treatment (cimetidine therapy) and one of a homeopathic intervention (calcarea carbonica). The review found no evidence either for or against the most commonly used treatment options for MC, and concluded the review by recommending well-designed, prospective, blinded randomised controlled trials on common treatment options for MC against a credible placebo or no intervention. These recommendations were based mainly upon the small size of studies that were included in the review that offered limited power within treatments arms and also the methodological shortcomings of those studies. Highlighting clearly that 'no treatment' is not recommended based upon ineffectiveness in treating MC but that previous research studies have been insufficient in providing a well conducted study providing results of an effective treatment.

1.1.7 At risk populations

MC mainly affects three distinct populations; children (8), sexually active adults (18) and those who are immunocompromised. The latter group consists primarily of those with Human Immunodeficiency Virus (HIV) infection (19). Overall MC is most prevalent in children, who are generally healthy and school aged (9). Strikingly this is also the group where there has been relatively little epidemiological data published. This is in contrast to sexually active and immunocompromised adults, where there is more published data. This may be due in part to adults having their MC diagnosed in GUM and specialist clinics (20), where there is a large amount of routinely collected data available for analysis.

1.1.8 Risk Factors

Some studies have suggested an association between an increased risk of a child developing MC and swimming, atopic eczema (AE), geography and climate (7, 21, 22), but provide only anecdotal evidence. Often data are presented from small studies as proportions without robust statistical analysis being performed. None of these risk factors have been explored in children recruited from the UK.

1.2 Is there a gap in the knowledge in the description of the epidemiology of MC?

In this section I highlight the need for an updated review on the incidence, prevalence and risk factors associated with MC. Previous reviews have been published, but as I will highlight below, these have significant limitations and have produced inconsistent results.

Two recent reviews which described the epidemiology of MC found between 11 and 13 publications within their literature searches (7, 23). Nevertheless, these studies described MC in populations of children in diverse settings, such as New Guinea (1970's (21)), Japan (1980's (24)) and Mali (1990's (25)) that are unlikely to be generalisable to children living in Western Europe and North America. There is very little evidence available from the UK. Of the three published UK studies identified in these two recent reviews, one was published in the 1960's

describing children in Aberdeen (22), and two more recent studies extracted routinely collected data to describe primary care consultation rates of MC, both published in the 2000's (5, 26). Although routinely collected data can be a rich data source containing a large amount of information, it is limited with regard to the information that is captured within the data collection systems. In most cases these systems do not allow flexibility in capturing data from the perspective of the child or parents that also describe the presentation, time to resolution, behaviours, and QoL impact.

Many studies describing the epidemiology collect data from only children who consult to primary care or speciality dermatology centres and these can be subject to healthcare access biases where findings may not be representative of all cases that may exist in the community (27). Children who consult with MC may represent more severe cases of the condition compared to those children who are successfully managing the condition at home without visiting a physician.

Both of these reviews highlighted that there is little adequately designed epidemiological research that has been published for MC (7). The two reviews described above differ by the studies included within the searches, the analysis of data extracted from studies, and provide no suggestions of whether the findings are acceptable to Western European and North American populations. From this it seems there have been no recent reviews of the epidemiology of childhood MC that have systemically synthesised data from the original research articles to provide a concise and accurate description of the current epidemiology that can be applied to children residing in the UK.

Clearly there is little evidence describing the epidemiology of MC in UK children, meaning that current health information available to clinicians and parents describing presenting symptoms, the natural history and impact on QoL from the condition may not be adequate. It is also clear

from the most recent reviews conducted that there are disparities in what has been reported from previous studies.

1.3 Why is describing the epidemiology of MC important?

Parents who visit their GP have a thirst for information (28), and questions such as, “how common is it”, “why have I got it”, and “will it go away” (29), are likely to be common. Currently for MC there is little evidence available to both parents and clinicians to answer these questions.

The findings from epidemiological data can support clinicians in being able to provide parents with accurate information regarding the potential risk factors which would increase the risk of disease for an individual, and the time to resolution of the disease (30). Interestingly, the paucity of this epidemiological evidence in the UK is not limited only to specific conditions such as MC but there is a well described imbalance within the field of dermatology between basic science and describing the distribution of a disease and factors that may influence this (31).

1.4 Summary

MC is a common skin condition that is typically diagnosed in primary care following a clinical examination of the lesions, and presents most frequently in children. Risk factors which have been associated with a higher prevalence of MC in children are AE, age and swimming. In the UK there have been no studies in the scientific literature that have described the presentation, time to resolution and QoL of children with MC since a small study providing little data published during the 1960's. Recent reviews of world-wide publications of childhood MC differ in both the number of studies included and analysis of extracted data; this highlights a clear starting point of this thesis to conduct a systematic review of the epidemiology of childhood MC within the subsequent chapter.

The research within this thesis will be limited to only UK children, and will be conducted in the primary care and community setting. The evidence base for many skin conditions that are managed primarily in primary care comes from secondary care settings (32), and therefore is likely to be biased. MC is managed primarily in primary care, and therefore it is important to generate an evidence base from this setting.

1.5 Thesis Aims and Objectives

1.5.1 Aim

The overall aim of this thesis is to describe the epidemiology of MC in children. The main research question of this thesis is ‘what is the presentation, time to resolution and prognosis of MC in children?’

1.5.2 Objectives

To address this aim, the objectives of the thesis have been identified:

- a) Provide, within the subsequent chapter, a systematic review of the current literature describing the epidemiology of MC to highlight research gaps in current evidence.
- b) Describe the basic epidemiology of MC in a community cohort of children recruited in the UK. The cohort established will describe:
 - The presentation and time to resolution of symptoms of MC in UK children.
 - The impact of MC and impairment on quality of life.
 - Cases of transmission of MC between other children living in the same household.
 - Treatment and management of MC by doctors, and parents self-medicating.
- c) To develop a diagnostic tool which enables parents to identify whether their child has a current diagnosis of MC and which can be used for recruitment in a large epidemiological study.

- d) To evaluate the effectiveness of parents using the MC diagnostic tool to identify a correct diagnosis of MC when compared to an expert's diagnosis.
- e) To describe the current number of children who present to primary care in the UK and are diagnosed with MC in a longitudinal cohort. The cohort established will describe:
 - The age and sex variation of MC consulting to primary care in the UK.
 - Currently treatments prescribed when a child is diagnosed with MC.
 - The variation in the incidence of MC presenting to primary care in the UK by year and season.
 - Associations between MC and a history of atopic eczema.
- f) To understand the interpretation of QoL scores through a systematic review of common skin conditions, including MC, that have used the CDLQI.

1.6 Patient representation

Involving lay representatives in research is important as it has been shown to improve the quality of the research. There are many benefits that a lay perspective can bring to research through their insights which may otherwise have been overlooked, and they can act to counterbalance ideas that may dominate from academic researchers (33). Input of lay representatives is varied and can be through several areas of the research process, such as helping to adapt academic language, and improving the wording of patient information and invitation letters (34). A lay representative, Ms. Samantha Woods (SW), was appointed to participate in bi-monthly supervisor project meetings which took place at Heath Park, Cardiff. If SW was unable to attend meetings feedback on patient documentation or specific areas of the project would be discussed by email or telephone. SW was recruited through 'Involving People' (NISCHR), where an advert was placed for parents who have children who have a current diagnosis of MC to be involved in this research. An advert was placed in early 2012, and SW was added to the research team by mid-2012. The organisation 'Involving People'

provided expenses towards the costs of attending the meetings such as travel costs and also a small token payment per hour for involvement in meetings.

1.1 The MOSAIC study

The MOSAIC study [**M**olluscum cont**A**giosum **I**n the **C**ommunity] was developed for this thesis. The MOSAIC study consisted of three study phases that are described in chapters five, six and seven. The study title and logo were used on study materials, the study website, communication with NHS ethics, local health boards and participants (Figure 1). All references to ‘the MOSAIC study’ within this thesis refer to the title of this clinical research study.

Figure 1. Example of MOSAIC study documents using the study logo



1.2 Approvals, governance, funding and study reporting

Copies of formal communication and approvals can be found within Appendix 5.

1.2.1 Ethical approval

The research was granted a favourable ethical opinion by the ‘NRES Committee South Central – Berkshire B’ research ethics committee (Ref: 12/SC/0455).

1.2.2 NHS research governance approval

Cardiff & Vale University Health Board granted research governance approval for practices within the health board. I was also issued with a letter of access for research practices (chapter six). Approval was granted by all health boards within wales for GP practices and secondary

care dermatology outpatient clinics to act as participant information centres (PICs) (chapter seven).

1.2.3 Study sponsorship

The study was sponsored by Cardiff University (Ref: SPON 1131-12).

1.2.4 National registration and reporting

The study was a UK clinical research network (UKCRN) adopted study within the skin portfolio (UKCRN Ref: 13430). Monthly recruitment data was submitted to the UKCRN database whilst the study was actively recruiting participants.

1.2.5 Funding

The research within this thesis was funded as part of a postgraduate research studentship by the Cochrane Institute of Primary Care and Public Health and School of Medicine, Cardiff University (Ref: BX1150NF01).

1.2.6 Study support costs

Service support costs were sought and obtained from the Wales School of Primary Care Research (WSPCR – NISCHR CRC); the total grant awarded was £15,890. The allocation towards the validation of the parental diagnostic tool (chapter six) was £10,500; practices were paid £35 per GP assessment at each site. This cost was to compensate the practice for clinical time spent with the participant, for local management of the study by identifying potential participants, collecting data forms, and returning completed study forms. £3,000 was allocated to compensate participants who were recruited to the prospective cohort study of children (chapter seven); each participant who completed the study questionnaires received a £10 high street gift voucher. An additional £2,000 was allocated to the study website that hosted the parental diagnostic tool and collected data from questionnaires which was secure and

conformed to data protection laws. A further £390 was allocated for additional study equipment.

1.3 Thesis synopsis

This chapter has outlined the background of the thesis.

Chapter two describes the methods and results of a systematic review of the published scientific literature describing the epidemiology of MC in children.

Chapter three describes a review of common skin conditions that have used the children's dermatology life quality index (CDLQI); a validated questionnaire measuring QoL in children presenting with dermatological conditions. The CDLQI will be used later in the thesis (chapter seven) to measure QoL in children with MC and this review will allow the results from this thesis to be presented and compared in relation to the QoL impact from other common skin conditions.

Chapter four presents the methods and results from a longitudinal study of primary care consultations for MC. Routinely collected data are extracted to describe recent trends of consultations and associations with other skin conditions.

Chapter five and six will describe the development and assess the extent to which a parental diagnostic tool for MC is a valid instrument to be used for recruitment in a large community based epidemiological study (chapter seven).

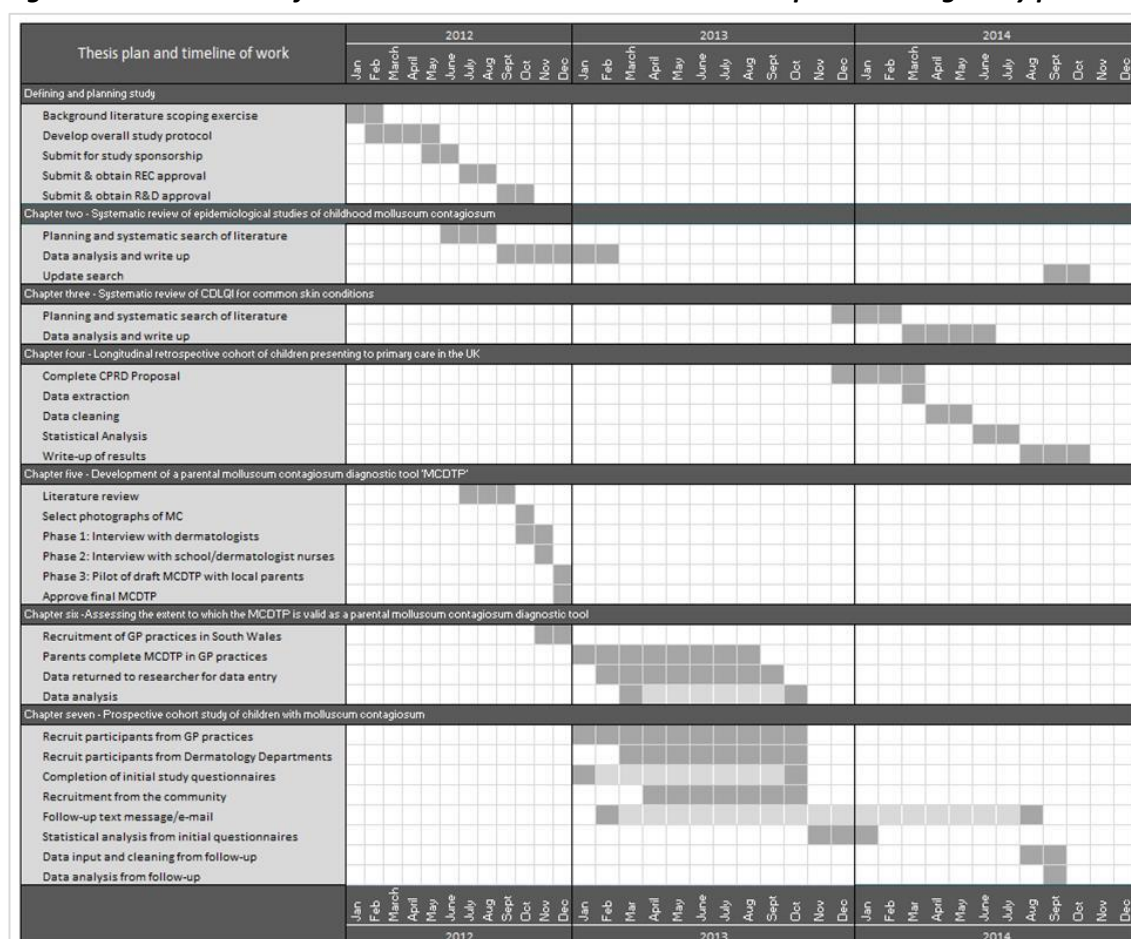
Chapter seven recruits a prospective cohort of children with MC to describe the presentation, management and advice, and QoL. Participants are followed up for the duration of their conditions to describe transmission and the time to resolution of symptoms.

Chapter eight is the final chapter of this thesis and provides a summary of the main research findings, a summary of the main limitations and potential biases of the methods used within

this thesis, and places the results in context to those from other relevant published literature. The chapter concludes by highlighting clinical management implications and future research recommendations.

A GANTT chart is presented in Figure 2 showing how the individual studies within this thesis were completed during the three year time period that this thesis was conducted.

Figure 2. GANTT chart of individual studies within this thesis completed during study period.



Chapter two: Systematic review of epidemiological studies of childhood molluscum contagiosum.

The results from this chapter were published as a systematic review in *Family Practice*. A copy of this paper can be found in Appendix 1.1.

2. Overview

MC is a common skin condition which regularly presents and is managed within both primary and secondary care, however the reported incidence and prevalence of MC varies widely in the most recent published reviews of the condition, therefore it is difficult to estimate the true number affected by MC. Evidence of factors increasing the risk of transmission is mixed. In this chapter I aim to synthesise the current epidemiology of childhood MC.

The chapter will firstly describe how prevalent MC is; whether there have been recent studies conducted within the UK, and, if not, whether the results from studies outside of the UK are generalisable to the UK population. Secondly the incidence of children presenting to primary or secondary care providers will be described, and associations with age and gender. Finally the chapter will describe the presentation of symptoms and risk factors associated with children presenting with MC in both primary and secondary care, and in the community.

Studies describing the QoL effect from MC using the CDLQI are included within a systematic review in the subsequent chapter (chapter three).

2.1 Design

This is a systematic literature review of bibliographical databases on the prevalence, incidence, risk factors, age distribution and association with other conditions for MC in children.

2.2 Search Strategy

I conducted a systematic search of bibliographical databases using a pre-defined search strategy in October 2012. Papers were also identified from reviews of citations within papers, a preliminary scoping exercise using 'Google Scholar', and identification of papers by experts in the field.

Medical subject headings (MeSH) were used in Ovid^{SP 1} to search the Medline (1946-October 2012), Embase (1947 – October 2012) and Cochrane databases (for MeSH terms please see Appendix 2.1). Duplicates were removed and the search was restricted to English language and studies involving humans. The search was performed again in October 2014 to identify whether there had been any further publications since this initial search.

2.2.1 Data extraction and analysis

All publications identified in the search were screened by title and abstract using the inclusion criteria below. The full texts of all articles which may have potentially been relevant were requested for full review using a template covering key study characteristics, incidence and prevalence of MC, age distribution, risk factors and other conditions associated with MC.

2.2.2 Inclusion and Exclusion Criteria

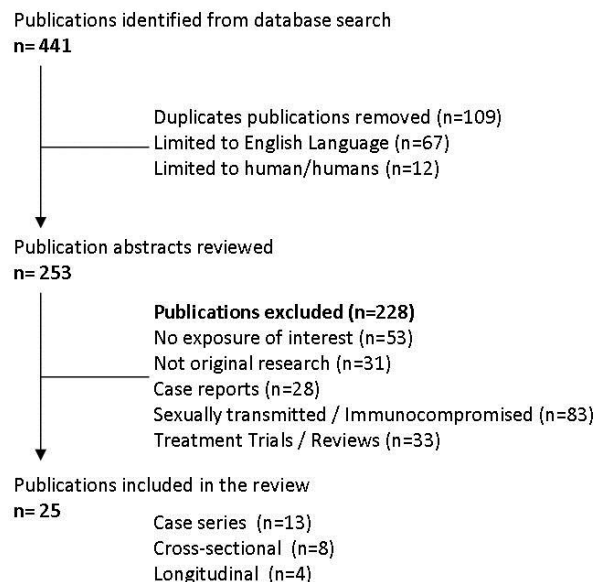
Papers were included if they were original research articles on the incidence, prevalence, risk factors, age distribution or other conditions associated with MC in children. I excluded studies if they were non-original research, review papers, singular case reports, treatment trials, or related exclusively to adults, immunocompromised individuals, those attending sexual health clinics, or dental MC. I included studies if they related to both children and adults, and where possible extracted only the data that pertained to children.

¹ OVID^{SP} provides access to online bibliographic databases and journals in the field of health sciences.

2.2.3 Search results

The search identified 441 papers. After reviewing the abstracts of all 441, 25 publications met the inclusion criteria (Figure 3). Data, where available, was extracted for analysis.

Figure 3. Flow chart of study selection process



The search was duplicated in October 2014 to identify whether there were additional publications since the initial search of bibliographical databases (October 2012). This search identified one additional publication that met the inclusion criteria, this was a longitudinal study and the data from within this publication are included within this chapter. Therefore, in total 26 publications are included in the review.

2.3 How prevalent is MC?

2.3.1 Definition of Prevalence

Prevalence measures a slice through the population at a certain point in time to determine who has and who doesn't have the disease/condition in question. The calculation of prevalence is performed by dividing the number of people affected by the condition, by the number of persons in the population at that time (30). This calculation measures the point prevalence of a disease, there is also a second measure called period prevalence. Period

prevalence accumulates all cases during a period of time, including those who developed, and may be symptom free, by the total population. The important aspect in this calculation is that it includes all individuals who have had or currently have the disease during the time period. It must be noted however that prevalence does not determine when a disease developed but that the disease was present during the time frame being measured.

Prevalence is often presented as a rate, but by strict definition it is a proportion of individuals who are affected by the disease in the population (35).

2.3.2 Summary of worldwide prevalence studies of MC

The prevalence of MC was described in eight papers (Table 1) however no papers reported the prevalence of MC in Western Europe or North America. Studies reporting the prevalence in children in a variety of settings in Israel, Romania, New Guinea, Mali, Japan and Turkey described a prevalence of MC ranging from 0.27% in six to 12 year olds in Romania (36) to 34% in two to nine year olds in Israel (37).

Table 1. Prevalence studies of MC (worldwide)

Ref	Location	Age Group (years)	Population	Cases	Prevalence	95% Confidence Interval (CI)
Sturt (1971) (21)	New Guinea	0 to 10	78	17	21.8	12.6 to 31.0
Niizeka (1984) (24)	Japan	4 to 11	7472	517	6.9	6.3 to 7.5
Oren (1991) (37)	Israel	2 to 9	81	28	34.6	24.2 to 44.9
Mahe (1995) (25)	Mali	0 to 12	1817	65	3.6	2.7 to 4.4
Popescu (1999) (36)	Romania	6 to 12	1114	3	0.3	0 to 0.6
Tuncel (2005) (38)	Turkey	14 to 16	166	2	1.2	-0.5 to 2.9
Tabari (2007) (39)	Iran	1 to 5	986	21	2.1	1.2 to 3.0
Hayashida (2010) (40)	Japan	0 to 6	913	180	19.7	17.1 to 22.3

The study population which is most similar to Western Europe and North America, in terms of economic development, is Japan, where two studies reported prevalence of 6.9% (1984) (24) and 19.7% (2010) (40). The largest prevalence of MC (19.7%) was reported in a cross-sectional study of children where parents were asked to recall a current or previous diagnosis of MC for their child. This may overestimate the point prevalence of MC as it includes any previous diagnoses', and relies upon accurate recall by parents (40). Similarly, the second study (prevalence 6.9%) also questioned parents about a diagnosis of MC, the authors did not report how a diagnosis of MC was obtained or if it was a current diagnosis (24).

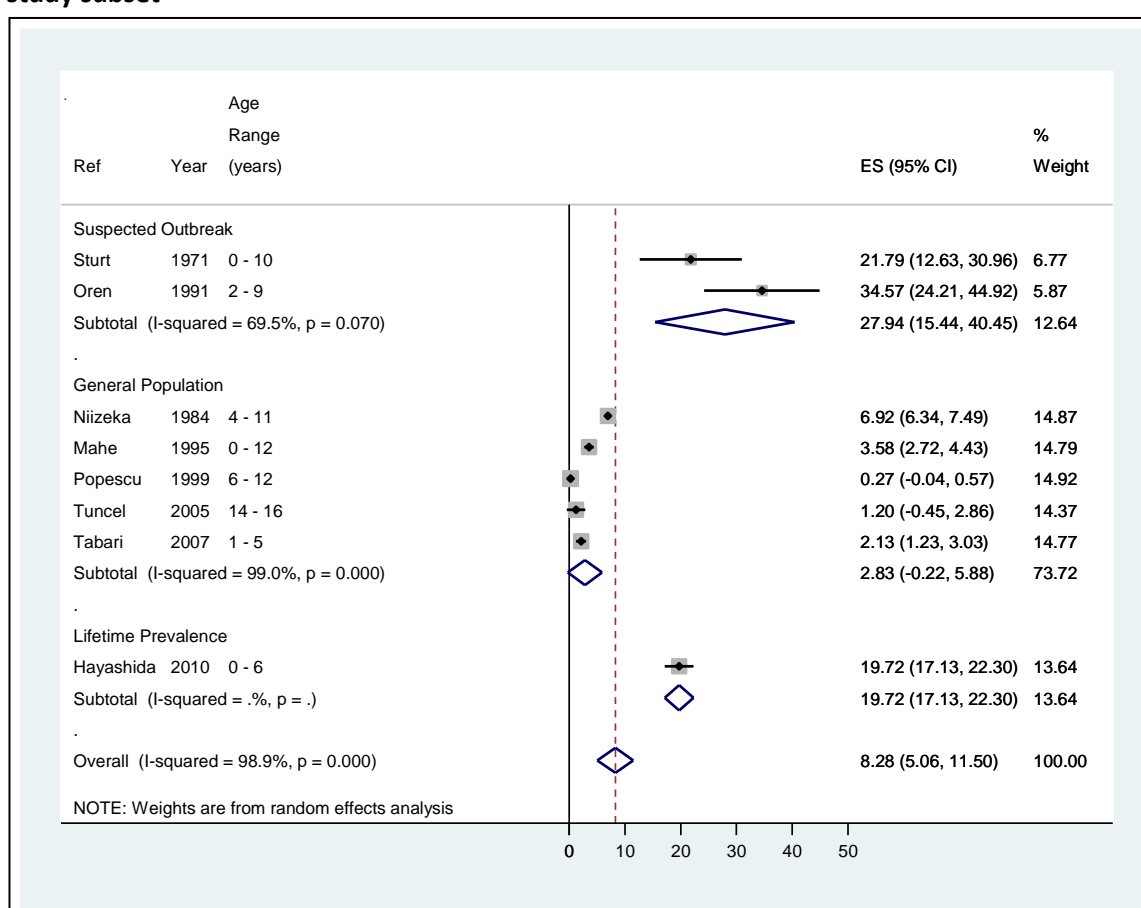
Two studies showed an exceptionally high prevalence of 34% and 22%. The first of these was conducted in a small rural community in the warm and dry climatic area of the Jezreel Valley, Israel following reports of a small epidemic in 1991 (37). The other was a study of 16 villages in the West Sepik District of New Guinea (21). Both of these studies concluded that the warm and dry climates of the areas under study were likely to have resulted in the unusually high prevalence rates found. However, the first study was described as taking place during an epidemic and the second had large variation in prevalence between individual villages, and therefore it can be questioned whether the results of either are representative of warm, dry areas. Indeed, studies from other warm and dry climates such as Mali (3.6%) (25), Turkey (1.2%) (38) and Iran (2.1%) (39) have reported considerably lower prevalence.

The lowest prevalence reported was 0.27% in Romanian school children, where each child had two independent paediatric assessments by dermatologists (36). Although the study did have robust methods in the diagnosis of MC it only included children aged between six to 12 years, and therefore did not include those at greatest risk (under fours (as shown later in incidence section)).

The remaining prevalence studies were conducted in Mali (3.6%) and Iran (2.12%) where these populations do not allow for a direct comparison with that of Western Europe and North America due to significant cultural and climatic differences.

Meta-analysis of prevalence data gives an overall estimated weighted prevalence in children of 8.28% (95% CI 5.1 to 11.5) (Figure 4), this figure may be skewed by the three studies reporting a considerably higher prevalence of MC due to potential outbreaks and a lifetime prevalence recorded. Where these studies are excluded the estimated prevalence is lower 2.83% (95% CI 0.0 to 5.9) (Figure 4).

Figure 4. Comparison of prevalence of childhood MC reported in cross-sectional surveys by study subset



2.3.3 Summary of Prevalence Studies

The reported prevalence of MC varies widely between 0.27% to 34.6%. Two studies reported a high prevalence of 22% and 34% in children. Due to the occurrence of a small epidemic, with a

relatively low sample size, in one study and the unexplained variation in prevalence rates between villages of similar climates and demographics of the second, these figures are not generalisable to other populations. The authors of both studies concluded that the high prevalence of MC was associated or caused by the warmer climate of that area but provided no further evidence of this. The prevalence of MC in other warm and dry climates such as Mali (3.6%) (25), Turkey (1.2%) (38) and Iran (2.1%) (39) have reported considerably lower prevalence and from this we can summarise that there is insufficient evidence to conclude that a warm and dry climate is a risk factor for a higher prevalence of MC.

Each of the prevalence studies have limitations which do not allow the prevalence rates to be generalised to a population within the UK, and where estimates are limited to only those conducted in the general population, the actual rate may lie between 0.27% to 5.88%. Until a comprehensive prevalence study is conducted within the UK, the most accurate data available to measure the number of children who have a MC diagnosis could be provided by longitudinal studies. Longitudinal studies extract routinely collected data to describe consultation or incidence rates of children presenting with MC to physicians; in the UK this is primary care centres. These study designs are particularly informative due to generally having a large and inclusive population.

2.4 What is the Incidence of MC?

2.4.1 *Definition of incidence*

Incidence is a measure of the proportion of a group of at risk individuals, within a population who are initially free of the disease or new outcome, who then go on to develop a certain condition being measured during a specified time period (41). The critical element of the definition is that it identifies *new* cases in those who were initially symptom free at the start of the study period (30). Incidence is usually presented as a rate of development of a disease by the total population subset over a set period of time (42) and the denominator used for

calculating an incidence rate will be identified at baseline, where it is from this group that any new cases of disease will be measured (30).

2.4.2 Summary of worldwide incidence studies of MC

There are five longitudinal studies which describe the incidence of MC consultations using routinely collected data. Two of the studies were conducted within the UK, two in North America, and one in Holland (Table 2).

Table 2. Incidence of MC

Ref	Data	Age Group (years)	Population	Sex	Annual Incidence (per 1,000)	95% CI
Konning (1994) (43)	1987-88, Holland	10	-	M&F	25.0	-
Pannell (2005) (5)	1994-03, United Kingdom	1 to 4	119,920	Male	15.0	14.4 to 15.8
			113,682	Female	15.2	14.5 to 16.0
		5 to 14	321,624	Male	10.7	10.4 to 11.1
			306,015	Female	10.5	10.1 to 10.8
Reynolds (2009) (44)	2001-05, North America	<1	-	M&F	1.9	-
		1 to 4	-	M&F	7.7	-
		5 to 14	-	M&F	3.1	-
Schofield (2011) (26)	2006, United Kingdom	1 to 4	-	Male	17.2	-
			-	Female	15.5	-
		5 to 14	-	Male	9.5	-
			-	Female	10.7	-
McCollum (2014) (45)	2001-09, North America	<1	-	M&F	1.9	-
		1 to 4	-	M&F	7.8	-

Notes: - data not reported.

2.4.3 Incidence of MC reported in the UK

Two incidence studies of MC have been conducted in England and Wales, both extracting data from the weekly returns of the Royal College of General Practitioners of primary care consultations. The first study by Pannell (2005) used data from 1994 to 2003 to calculate incidence rates for a MC diagnosis recorded by a GP (5). The largest incidence was in those

aged one to four years, and females had a slightly higher incidence compared to males (15.2 and 15.0 per 1,000 respectively), however this was not significant. The five to 14 year age group had slightly lower incidence rates (males 10.7 and females 10.5 per 1,000), and again there were no significant differences between gender.

Schofield (2011), analysing data from the same source as Pannell, described the incidence of MC during 2006 (26). The incidence in males aged one to four were higher than those reported by Pannell (2005) (17.2 per 1,000), although females did rise to 15.5 per 1,000, but not significantly. Using the same age groups as Pannell (2005), the five to 14 age group males has slightly lower incidence rate than those previously reported (9.5 per 1,000), and in females they had risen slightly to 10.7 per 1,000.

Pannell described trends in the incidence of MC, reporting a 50% increase from 1994 to 1999 of 8.0 to 12.0 per 1,000 in those aged one to 14 years. The results seem to decline or steady from 1999 to 2002, although the poor presentation of figures by the authors does not allow for detailed analysis. Incidence rates in those aged 15 and over remained constant during the study period, and when monthly incidence rates were explored they show variation but no link to temperature or seasonality were reported.

2.4.4 Incidence of MC reported world-wide

The largest incidence of MC was reported in Holland as 25 per 1,000, where data was extracted from 10 Dutch general practices with a total study population of 332,300 (43), although this figure is calculated only for those aged 10 years. Regional differences were found in the incidence rates in regions of Holland, ranging from 1.0 to 3.2 per 1,000 between three regions. The author noted no differences in the climate, temperatures or urbanisation between the areas, with very similar rates reported in each population size examined. Regional differences were also found in two studies in North America (44), where differences were

consistent in the five and nine years of study data examined and, again, there was no explanation that could attribute a higher incidence to a region.

In North America, two studies examined the annual incidence rate in outpatient visits for MC. Both studies extracted data from the Indian Health Service, which is representative of 57% of the American Indians/Alaskan Natives (AI/AN) population in North America. Reynolds (44) examined data for the period 2001 to 2005 where the greatest incidence was in children aged one to four years (7.7 per 1,000). Similarly, McCollum (45), who included a further four years of data in their analysis (2001 to 2009), provided only a marginally higher rate for the same age group (7.8 per 1,000). The latter study included only children aged less than five years. Both studies found no differences in the incidence of MC between genders.

2.4.5 Summary of the incidence of MC

In all ages the greatest incidence of MC was in children aged zero to 14 years. Where age ranges were analysed further within this zero to 14 year age group, the highest incidence was found in those aged one to four years. It can be concluded that there is no difference between incidence rates for gender.

Each study produced incidence rates by different age categories, some narrower than others which does not allow direct comparison between the groups. The two studies within the UK analysed rates by zero to four and five to 14 aged children, and this may have been due to the limitations of the database for extraction as both used the same source (5, 26), but it did not provide further expansion of incidence rates within the five to 14 year age group. As MC is most common within these age groups, the use of narrower age groups would be beneficial for a more detailed description of what aged children are most at risk of MC.

There were regional differences found by Koning (43), Reynolds (44) and McCollum (45), and no results by region were produced in the two UK studies. Koning, Reynolds and McCollum

showed there were geographical regions that had a higher incidence rate of MC than others, but none could determine a cause. Urbanisation was modelled in Koning's analysis and showed no differences between the population densities of the area. All three authors described there were no significant climatic differences between the regions to account for a difference in incidence; however this was not factored into their analysis.

The difference between the incidence of MC reported in Western Europe and North America may be due to the different healthcare systems in the two continents, the Western European studies recorded data where patients had visited a GP, which is first point of contact for all non-emergency patients. Data extracted in North America included only outpatient visits to a specialist physician, which was exclusive to the AI/AN population, and is not representative of the North America population.

In conclusion, the largest incidence of MC is in children, aged between zero to 14 years. Where results are combined the incidence expected is shown to be 12 to 14 per 1,000. Incidence rates in the UK were beginning to steady from 1999 to 2002, and a more recent single-year study in 2003 showed the rates had slight decline. Current rates have not been explored to determine if rates have declined further or to provide a detailed analysis of age groups within those aged zero to 14 years. Studies outside the UK have shown regional variation in incidence rates, and although they have provided no conclusive reasoning for this, there would be merit in modelling this into a future incidence study.

2.5 Presentation and prognosis of symptoms

2.5.1 Age

In a large cohort of Greek children (n=4071) of children consulting to a dermatology outpatient clinic, the peak age of children with MC was four to six years (46). This study did not include children over the age of 12 years; nevertheless the results were comparable to those of a

similar study of 650 French children aged zero to 15 years, where the peak age of individuals was six years.

Age was further described in seven studies of children consulting with MC (3, 11, 22-24, 47, 48), and the peak or mean age lay between five to 12 years (Table 3). There was large variation in the age range of the sample recruited in each.

2.5.2 Gender

There was no evidence of a difference in prevalence by gender for children who consult to a dermatologist with MC, with the proportion of males ranging from 41.2% to 62.0% and confidence intervals including 50% in most studies (Table 3).

2.5.1 Time to resolution

The typical time to resolution of symptoms described in literature ranges considerably from several months to five years (2, 9, 49, 50). However, from this search there were only two studies, of small sample size, to have followed up cases of MC to describe the time to resolution during the 1960's in children who consulted with MC. Alaska (n=13) and Fiji (n=14) reported the time to resolution that ranged from 2 weeks to 24 months (13). The mean time to resolution was calculated only in Fiji as 8 months (47).

Table 3. Characteristics of children and natural history of MC

a) Age					
Ref	Sample	Age Range (years)	Peak Age (year)	Measurement used	
Sturt (1971) (21)	401	0 to 57	2	Peak	
Niizeka (1984) (24)	405	4 to 11	8	Peak	
Oren (1991) (37)	34	2 to 31	5	Median	
Castilla (1995) (51)	24	4 to 13	9	Median	
Choong (1999) (11)	198	0 to 47	8	Average	
Osio (2011) (52)	650	0 to 15	6	Mean	
b) Gender					
Ref	Sample	Male	Female	Proportion males	95% CI
Sturt (1971) (21)	401	217	184	54.1%	49.2 to 58.9
Oren (1991) (37)	34	14	20	41.2%	26.4 to 57.8
Castilla (1995) (51)	24	16	8	66.7%	46.7 to 82.0
Choong (1999) (11)	198	86	112	43.4%	36.7 to 50.4
Kakourou (2005) (48)	110	60	50	54.5%	45.2 to 63.5
Braue (2005) (23)	30	17	13	56.7%	39.2 to 72.6
Dohil (2006) (3)	302	145	155	48.0%	42.4 to 53.6
Tabari (2007) (39)	21	13	8	61.9%	40.9 to 79.2
Kuchabal (2010) (53)	100	62	38	62.0%	52.2 to 70.9
Osio (2011) (52)	648	330	318	50.9%	47.1 to 54.8
c) Time to resolution of lesions					
Ref	Sample	Age Range (years)	Median (months)	Range (months)	
Overfield (1966) (13)	13	0 to 14	-	0 to 18	
Hawley (1970) (47)	14	3 to 11	8	0 to 24	

Notes: - missing data.

2.5.2 Quality of life

QoL can be impacted on greatly by dermatological conditions (54), although there are few studies specifically describing the impact upon QoL from MC. Where children and parents (n=30) completed QoL questionnaires when attending primary or secondary care consultation for MC, parents were significantly more concerned about MC than their child, 82% of parents (n=23) stated 'it concerned them moderately or greatly', compared to 43% of children (23). No

information was given of the validity of the QoL questionnaire which was used in the study, and there was no comparison of these results to other dermatological conditions.

Studies reporting QoL using the CDLQI are reported in the next chapter in the systematic review of common skin conditions that used the CDLQI.

2.6 What are the reported risk factors of MC?

2.6.1 Swimming

Table 4. Association between swimming and MC

Ref	Controls (num)		MC positive (num)		Relative Risk	CI (95%)
	Sample	History of swimming	Sample	History of swimming		
Postlethwaite (1967) (22)	1848	915	13	13	-	-
Niizeki (1984) (24)	24	4	24	12*	2.0	1.25 to 3.20
Castilla (1995) (51)	6995	5925	517	481	2.3	1.65 to 3.21

Notes: - missing data. *High frequency swimming pool use

Swimming was firstly discussed by Wilson (1910) as an activity causing an increased opportunity for transmission of MC (55), and from the published data it is clear there is an association between a recent history of swimming and development of MC in children (Table 4).

Comparing swimmers against non-swimmers, showed a strong association (RR 2.3 (95% CI 1.65 to 3.21)) (51), and the relative risk was similar to that which compared high to low frequency swimming pool use (RR 2.0 (95% CI 1.25 to 3.20)) (24). It was not possible to calculate relative risk using data from a third study, however all children with a positive diagnosis of MC (n=13) did swim (22).

An association was shown between swimming pool based activities, bathing and a more severe case of MC (> 26 lesions), specific activities being; using a school swimming pool (RR 1.86 (95%

CI 1.79 to 3.37)), sharing a bath sponge (RR 2.79 (95% CI 1.69 to 5.43)), and sharing a bath towel (RR 1.57 (95% CI 1.33 to 3.67)) with someone infected with MC (11). The cohort recruited in this study (n=210) consisted of persons aged zero to 47 years, this may skew the results as the risk factors described would be typically associated with school aged children who are more at risk of developing MC. The study does not show an increase risk of developing MC, but that children may have a more aggressive infection due to these specific activities.

2.6.2 *Transmission between family members*

Only one study described the incidence of MC in children in a household of an index case. A small number of children (n=8) were followed-up for the duration of their lesions during the 1960's, and reported two cases (n=2/8) where there was development of lesions in other family members (13). Although this does provide a description of development of lesions between family members, this is a relatively small sample and it was unknown if all eight cases did indeed have siblings.

2.6.3 *Associations with atopic eczema (AE)*

A group of children in Greece (n=110) with MC were compared to a previous national study to examine prevalence of AE between the two groups. 18.2% (n=20) of the MC cohort had AE compared to the results of the national survey of 5% (48). Although the data from this study illustrates the prevalence of AE in children with MC as high, the national survey examined children aged one to six years whereas the cohort of children attending the dermatology clinics were aged between eight months and 11 years, therefore not allowing a direct comparison. In North America the case notes of children attending paediatric outpatient clinics were prospectively reviewed (n=302) and showed a slightly higher proportion of children with MC (24%) also having AE (3). In France, a larger proportion of children with MC were shown to have a history of AE 43% (n=279) (52). North American children, aged less than five years with

a current MC diagnosis (n=84) were more likely to have had an AE diagnosis (n=109) (odds ratio (OR) 2.51 (95% CI 1.1 to 6.0) p=0.029) and more likely to have had or have a current AE diagnosis (OR 3.58 (95% CI 1.77 to 7.52) p< 0.05) than controls.

A prospective observational study in a paediatric outpatient clinic in Brazil (n=284) suggested no relationship between MC and the development of AE (56) in children presenting with MC and/or AE; where the prevalence of MC in those with AE was 18.2% (n=38/209), and AE in those with MC 33.6% (n=38/113). However, an association was described between having a higher number of lesions and developing AE (p=0.045).

2.6.4 Summary of presentation, QoL and risk factors

All studies in this review showed the peak age would lie between 4 to 12 years, and the studies consisting of the largest number of children (46, 52) showed the mean age of children with MC to be in those aged 4 to 6 years. There were no differences in those presenting with MC between genders.

There were two studies which described the time to resolution of lesions in children during the 1960's, both of these were of small sample sizes (Alaska:n=13 (13), Fiji:n=14 (47)). Highlighting that there is little evidence to describe the time to resolution of MC or estimate the prognosis in children who develop symptoms, and a clear gap in the scientific literature.

Where a small number of parents and children were asked to complete a QoL questionnaire (23), the findings showed that MC was a concern for both. A universally validated instrument was not used, therefore not allowing for QoL comparisons between other dermatological conditions.

The associations between swimming and a higher risk of MC development have been described often within the literature. Postlethwaite (22), Niizeki (24), Castilla (51), and Choong (11), all showed that swimming was common in those with MC. Where relative risk has been

calculated it indicates that swimming is a causal factor for development of MC in children. The sharing of towels and bath sponges with someone infected with MC was shown to increase the risk of having a more aggressive infection of MC (11).

There is little evidence suggesting that children who have AE will develop MC during their childhood. Although the development of AE in children with MC is high and may lie between 18% to 43%, the likelihood of a current or previous AE diagnosis in children with MC compared to controls is high (45). The search found no studies that have examined the relationship between children with a previous episode of AE and if they are more likely to develop MC.

2.7 Discussion

The three sections within this literature review chapter provide a detailed review of published epidemiological data of childhood MC. In summary, the largest incidence of MC in all ages is for children. Combining data from different studies it showed there was an overall incidence rate in children of 12 to 14 episodes per 1,000 person-years. Incidence rates in the UK were greatest in those aged one to four years, and there was little variation between genders (5, 26). Current rates have not been explored to describe recent trends or to provide a detailed analysis of age groups within those aged zero to 14 years. These age groups may show different rates of MC due to the changing behaviours for younger primary school aged children compared to older children who are attending secondary school.

The analysis found an overall reported prevalence of MC in children of between 5.1% and 11.5%. Where gender of those attending specialist dermatologists were examined, there was little variation in numbers between males and females. There is evidence for an association between swimming and having MC and MC is more common in those with AE, however there is little evidence for other risk factors.

2.8 Limitations of systematic review

2.8.1 Potential limitations in the data collection methods

The data collection methods used to capture a diagnosis of MC varied considerably, in two studies in Japan there may be over estimate of the point prevalence due to the self-reporting of a diagnosis. One study includes any previous diagnoses, and relies upon accurate recall by parents (40) and another did not report how a diagnosis of MC was obtained (24). Where a robust diagnostic method consisting of two independent dermatologist examinations was used, it only included children aged between six to 12 years, and therefore did not include those at greatest risk (aged under four years - as shown in incidence section). The results of the meta-analysis may also be skewed by the three studies reporting a much higher prevalence of MC.

All studies on the incidence of MC used routinely collected data and this is subject to coding problems and under-ascertainment (2, 6, 57-64). Therefore, the true incidence of MC is likely to be considerably higher than reported in these studies. This is supported by the reported prevalence, especially in studies that involved examinations, compared to the reported incidence.

2.8.2 Potential limitations of the study populations

The association between MC and AE is not well described, and comparisons between the two are limited. Where the number of children with AE in a cohort of MC cases were compared to that of a national survey (48), they did not allow a direct comparison due to the different age groups; the national survey examined children aged one to six years whereas the cohort of children attending the dermatology clinics were aged between eight months to 11.5 years.

In the two studies in North America where data was extracted for the AI/AN population (44, 45) the results may not be generalisable to wider population due to the selectiveness of study population being limited to only AI/AN's.

Where swimming pool and bathing activities such as using a school swimming pool, the sharing of towels and bath sponges with someone infected with MC were shown to increase the risk of having a more aggressive infection of MC (11). The analysis in this study included both adults and children and as the risk factors described would typically only be associated with school aged children who are more at risk of developing MC, this may have skewed the results.

2.8.3 Potential biases of this review

2.8.3.1 Limiting search results to the English language

This systematic search of the literature was limited to only those published in the English language and therefore excluded non-English studies reporting the epidemiology of MC. Excluding studies based upon language could miss potentially important findings being reported within the results and this is a limitation of the results presented here. The limitation may be reduced as there is evidence that excluding research published in the non-English language are found to have generally little effect on summary effect estimates (27).

2.8.3.2 The effects of citation bias

The search results could have been affected by citation bias, whereby highly cited journals which are easy to find and often present at the top of search results are included within literature reviews and those which may prove difficult to find are potentially unjustifiably excluded. To avoid citation bias a systematic search of the most appropriate bibliographical databases was conducted that selected published research articles from all journals within the database that matched the search terms regardless of number of citations and place of publication.

2.8.3.3 Bias of the reviewer

A final potential limitation of the systematic review is that the search could have been influenced by the reviewer (myself) as only I reviewed the papers that were included within the search. It is common for search results to be reviewed independently by at least two reviewers, however due to the feasibility and availability of a second reviewer only I reviewed the papers and extracted data of those identified from the search. This may have reduced the validity of the results and the Cochrane Collaboration guidance for systematic searches recommends more than one reviewer to minimise errors and reduce potential bias introduced by reviewers (65). To provide transparency in the search methods, and conforming to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (66), the method of study selection including search strategy, process for selecting studies, and method of data extraction were provided explicitly in the methods and consistently adhered to. Papers were also discussed with JG² who advised on data extraction, any further analysis and the presentation of results.

2.9 Conclusions

- This systematic review highlights that data on the epidemiology of MC is of poor quality and this may be due, in part, to MC often being considered to be a trivial condition by some clinicians (2) and therefore there has been little research in the area.
- In the UK there have been no studies that have described the presentation, current management, transmission, impact on quality of life and time to resolution of MC.
- Summarising the available published data suggest the prevalence of MC in children aged zero to 16 years may lie between 5.1% to 11.5%.
- The greatest incidence of MC is for children aged one to four years; however the incidence in the five to nine age group has not been clearly described.

² John Gallacher (JG), Professor of Epidemiology and academic supervisor for this thesis.

- There are few data on the time to resolution but the best available data suggests that lesions last anywhere from 2 months to 2 years.
- MC appears to be more common in children who swim.
- Children with MC seem to have a higher prevalence of AE, the relationship between a previous diagnosis of AE and future risk of MC has so far not been reported.

The following chapter will conduct and report the findings of a systematic review of studies that have used the CDLQI to describe the impact of common skin conditions on QoL.

Chapter three: Systematic review of common skin conditions using the children's dermatology life quality index (CDLQI).

3. Overview

This chapter describes a second systematic review exploring studies that have used the CDLQI to describe QoL for childhood MC and other common skin conditions presenting in children. The overall findings of CDLQI scores by study and condition will be described, including a meta-analysis of these conditions which will summarise the weighted average CDLQI score for a condition and for all common skin conditions. A detailed description of QoL in children with MC that have used the CDLQI scores will be provided. Finally, the results will be summarised and I will discuss how these impacted the interpretation of results later in this thesis.

3.1 Children's Dermatology Life Quality Index (CDLQI)

The CDLQI was developed by academics within the Department of Dermatology at Cardiff University to measure the QoL in children with skin disease (67). The validity of the CDLQI in measuring QoL in children aged four to 16 years has been measured and found to be acceptable, and the instrument is available as a text or a cartoon version (68). Since its creation in 1995 recent publications have described the CDLQI being used in over 102 research studies (69) and it is the most widely used dermatological specific instrument for measuring QoL in children with skin conditions worldwide.

The CDLQI has been used in this thesis therefore it is important that the meaning and an understanding of a CDLQI score is provided prior to the interpretation of the results. Although a thorough review of the CDLQI use from its development was recently published in 2013 (69) this paper did not provide a pooled summary or meta-analysis of each condition's CDLQI score and compare this to other common skin conditions. By providing a meta-analysis of the mean CDLQI score of a range of common skin conditions it can aid interpretation between these

conditions and also provides a weighted average CDLQI score for individual and grouped conditions; therefore providing a more accurate representation of QoL effect.

3.1.1 Interpretation of CDLQI scores

The CDLQI is predominately used to mark changes in QoL between two time points during treatment trials or to describe the natural history of a condition where the main outcome of the research may be to provide the percentage change of a QoL score at different times for the same patient (67). For epidemiological studies where the aim is to measure QoL impact of the same condition within a large sample of children, the meaning of an overall mean CDLQI score is required to aid interpretation. Waters (2010) developed a severity stratification of CDLQI scores that can be used to interpret a CDLQI score (Table 5). This stratification was published as a conference abstract and therefore the full methodologies and validity of those scores are not provided in detail. However, this severity banding is widely used to interpret a mean CDLQI score within the scientific literature (69). The CDLQI severity bands developed by Waters will be used within this chapter and later in this thesis (chapter seven) to interpret CDLQI scores.

Table 5. Interpretation of CDLQI score by severity banding (70)

Score	QOL Effect
0 to 1	No effect
2 to 6	Small effect
7 to 12	Moderate effect
13 to 18	Very large effect
19 to 30	Extremely large effect

3.2 Literature search methods

3.2.1 Aim

The aim of this review is to compare the mean CDLQI scores from published data of childhood MC and other common childhood skin diseases.

3.2.2 Search strategy

A systematic search of bibliographical databases was carried out using a predefined search strategy in January 2014. Articles were also identified from citations within articles, from identification by experts, and from searching the online CDLQI bibliography (71).

The search term “CDLQI” was used in OVID^{SP} to search the Medline (1995 to January Week 2 2014) and Embase databases (1995 to January 2014) (1995 chosen as date CDLQI was first published). Duplicates were removed and the search was restricted to articles in English.

3.2.3 Data extraction and analysis

All publications identified were screened by title and abstract using the inclusion criteria stated in the following sub section. All potentially relevant articles were fully reviewed by myself using a template to record condition, study location, setting, study design, sample, and CDLQI score (mean, standard deviation (S.D.)).

3.2.4 Inclusion and exclusion criteria

Articles were included if they were original research articles of skin conditions that reported QoL using the CDLQI. I excluded studies if data was not presented at baseline in intervention studies, if data had been split by treatment arm, or overall CDLQI data was not presented. Studies were excluded where CDLQI and DLQI scores were combined as this has been shown to potentially invalidate results (72).

A list of articles that had been screened and met the inclusion criteria was produced. The list was discussed with a panel of two experts; NF³ and AYF⁴ who identified which conditions were ‘common’ or ‘uncommon’ and therefore should be included within the final analysis.

³ Nick Francis (NF), Clinical Reader and GP with expertise in skin conditions.

⁴ Andrew Finlay (AYF), Professor of Dermatology.

3.3 Results

3.3.1 Search results

The search identified 187 articles. After reviewing the abstracts of all 187 articles, 26 met the inclusion criteria (Figure 5). Within the 26 articles, CDLQI scores were given for 22 skin conditions. The following ten common conditions were included within the meta-analysis: acne (number of articles=4), AE (n=19), MC (n=2), naevi (n=1), psoriasis (n=7), pityriasis rosea (n=1), scabies (n=1), urticarial (n=1), vitiligo (n=4), and warts (n=2) (Table 6). The following uncommon conditions were excluded: alopecia, congenital ichthyosis, ectodermal dysplasia, epidermolysis bullosa, erythropoietic protoporphyria, hydroa vacciniforme, neurofibromatosis, photosensitivity disorders, pigmentary abnormality, scleroderma, vascular abnormality, and xeroderma pigmentosum.

Figure 5. Flow chart of study selection process

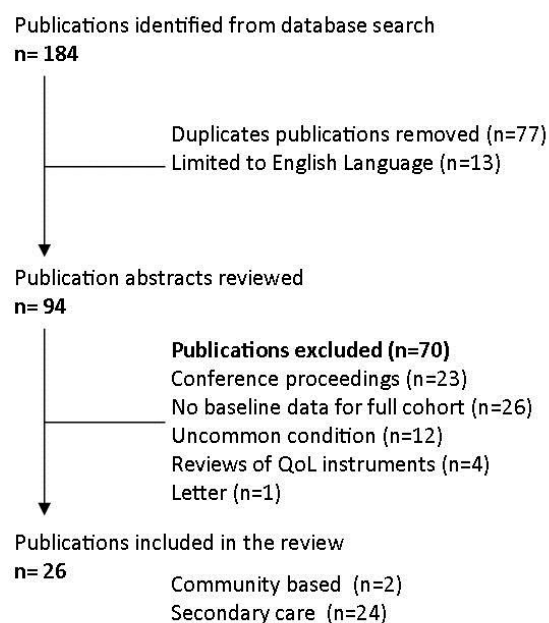


Table 6. CDLQI scores of common skin conditions by study, setting and design

	Ref	Ref Year	Location	Setting	Study Design	Sample Size	CDLQI Score (mean)	SD (±)
Acne								
	Beattie (73)	2006	UK	Secondary Care	Case series	50	5.4	4.69
	Jankovic (74)	2012	Serbia	Community	Cross-sectional	353	4.35	9.5*
	Lewis-Jones (67)	1995	UK	Secondary Care	Case series	40	5.7	4.4
	Walker (75)	2006	UK	Community	Cross-sectional	147	1.7	5.9*
Atopic Eczema								
	Hon (76)	2008	China	Secondary Care	Case-control	44	7.4	4.8
	Chinn (77)	2002	UK	Secondary Care	Case-control	120	7.9	6.1
	Chuh (78)	2003	China	Secondary Care	Case series	10	7.7	2.95
	Dertlioglu (79)	2013	Turkey	Secondary Care	Case-control	50	7.74	4.59
	Ganemo (80)	2007	Sweden	Secondary Care	Case series	50	7.1	4.4
	Holm (81)	2006	Denmark	Secondary Care	Case series	35	8 (median)	-
	Hon (82)	2007	China	Secondary Care	Treatment trial	28	8.7	5.4
	Hon (83)	2010	China	Secondary Care	Case-control	110	8.6	5.3
	Jirakova (84)	2012	Czech Republic	Secondary Care	Case series	48	8	4.98
	Kim (85)	2012	Korea	Secondary Care	Case series	415	6.6	6.3
	Maksimovic (86)	2011	Serbia	Secondary Care	Case series	64	12.74	6.29
	Amaral (87)	2012	Brazil	Secondary Care	Case series	52	9.5	7.8*
	Manzoni (88)	2012	Brazil	Secondary Care	Case series	50	9 (median)	-
	Noor Aziah (89)	2002	Kuala Lumpur	Secondary Care	Case series	33	10	6.6
	Shum (90)	2001	UK	Secondary Care	Case series	237	10.5	7.3*
	Sunderkötter (91)	2006	Germany	Secondary Care	Case series	1438	12.2	6
	Lewis-Jones (67)	1995	UK	Secondary Care	Case series	47	7.7	5.6
	Beattie (73)	2006	UK	Secondary Care	Case series	106	9.14	6.69
	Beattie (73)	2006	UK	Secondary Care	Case series	38	4.9	5.25
Molluscum Contagiosum								
	Beattie (73)	2006	UK	Secondary Care	Case series	14	3.07	3.58

	Ref	Ref Year	Location	Setting	Study Design	Sample Size	CDLQI Score (mean)	SD (±)
	Lewis-Jones (67)	1995	UK	Secondary Care	Case series	7	4.9	3
Naevi								
	Beattie (73)	2006	UK	Secondary Care	Case series	56	1.46	3.04
Pityriasis Rosea								
	Chuh (78)	2003	China	Secondary Care	Case series	10	3.5	1.18
Psoriasis								
	Beattie (73)	2006	UK	Secondary Care	Case series	29	9.17	7.83
	de Jager (92)	2010	Netherlands	Secondary Care	Case series	39	6 (median)	-
	Lewis-Jones (67)	1995	UK	Secondary Care	Case series	25	5.4	5
	Manzoni (88)	2012	Brazil	Secondary Care	Case series	25	7 (median)	-
	Oostveen (93)	2012	Netherlands	Secondary Care	Case series	125	7.5	5
	Oostveen (94)	2014	Netherlands	Secondary Care	Case series	34	9.6	5.4
	Paller (95)	2010	North America	Secondary Care	Case series	182	2.6	3.3
Scabies								
	Lewis-Jones (67)	1995	UK	Secondary Care	Case series	6	9.5	10.5
Urticaria								
	Beattie (73)	2006	UK	Secondary Care	Case series	17	6.12	6.39
Vitiligo								
	Dertlioglu (79)	2013	Turkey	Secondary Care	Case-control	50	11.68	6.54
	Njoo (96)	2000	Netherlands	Secondary Care	Treatment trial	51	5.6	3.8
	Manzoni (88)	2012	Brazil	Secondary Care	Case series	43	2 (median)	-
	Kruger (97)	2012	Germany	Secondary Care	Case series	51	2.8	3.8
Warts								
	Beattie (73)	2006	UK	Secondary Care	Case series	24	2.87	3.38
	Lewis-Jones (67)	1995	UK	Secondary Care	Case series	34	3.3	2.9

Notes: * Standard deviation not provided in published data, calculated using methods by Hozo (2005)(98) - Standard deviation not provided in published data and insufficient information to calculate.

3.3.2 Study design and geography

Of the 42 conditions that were extracted from the 26 published articles, the majority of data for these conditions were from case series studies of children attending a specialist dermatology centre (n=33 (78.6%)), five were case-control studies and the remaining four treatment trials (n=2) or cross-sectional studies (n=2). Over half of the conditions (n=27 (64.3%)) were described in children of Western Europe or North American countries.

Most studies contained data of just one condition, however two studies, both of UK children, used the CDLQI in children attending dermatology outpatient clinics to describe QoL from multiple conditions (67, 73).

3.3.3 CDLQI score of children with MC

Two similar studies in the UK provided CDLQI scores for children with MC (Table 6). Firstly children, aged four to 16 years, attending a paediatric dermatology clinic in Wales, UK were asked to complete the CDLQI during 1992 to 1993 (67) (younger children may be assisted by their parents when completing the CDLQI). 223 children provided complete CDLQI's, and seven of those had presented to the clinic with MC (four males, three females). The mean age of children with MC was 7.6 years and the mean CDLQI score was 4.9 (range 2 to 11) indicating a small QoL effect. A second study of children attending paediatric dermatology clinics in Scotland, UK recruited 379 children aged five to 16 to complete the CDLQI where they had experienced symptoms of their condition for over 6 months (73). Fourteen children with MC completed the CDLQI and had a mean age of 8 years. The mean CDLQI score was 3.07 and ranged between 0 to 11, indicating again a small QoL effect for children with MC.

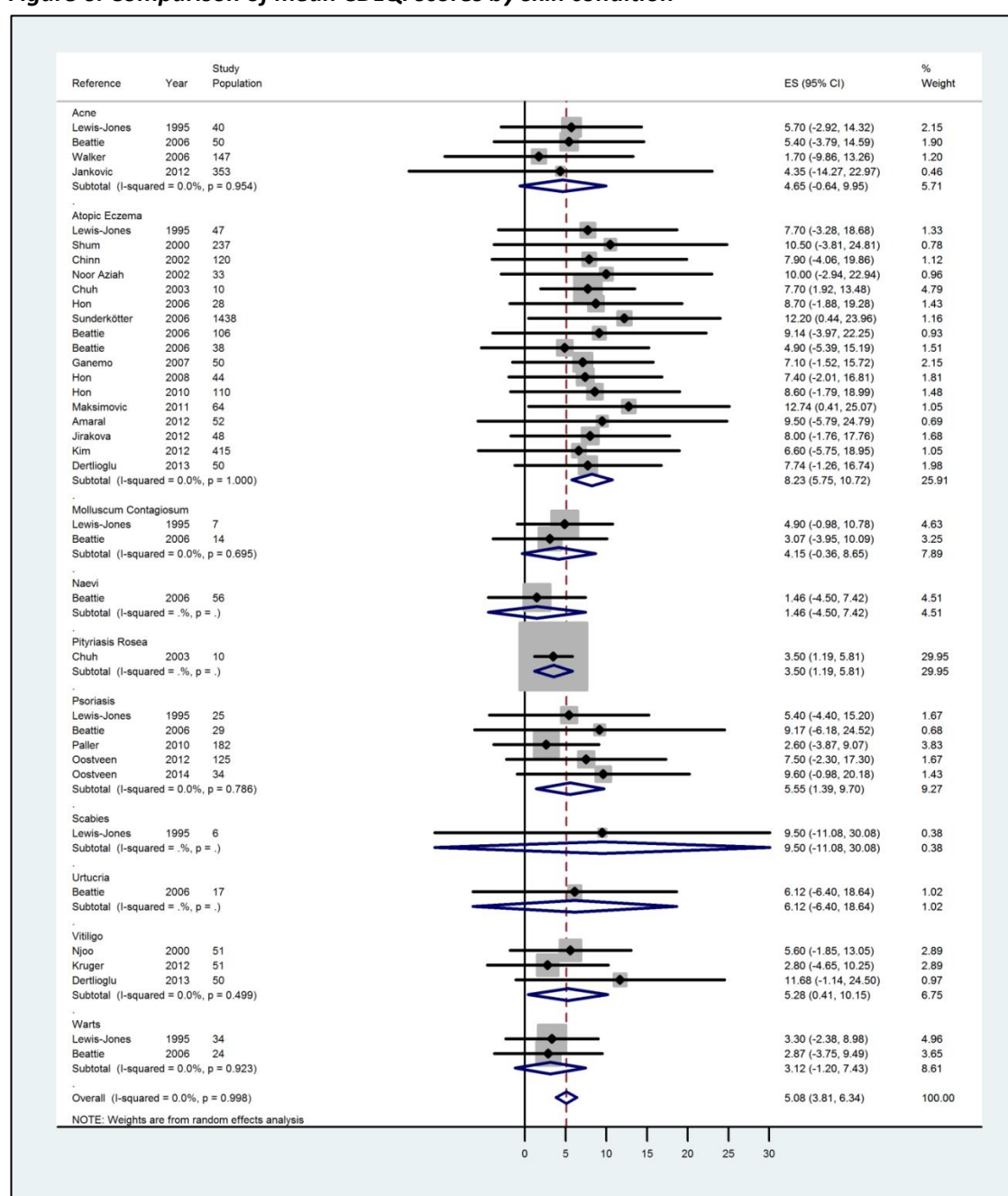
3.3.4 CDLQI scores for other conditions

The mean CDLQI scores of common skin diseases ranged between 3.9 to 6.5 (Figure 6), indicating that overall they have a small to moderate effect on QoL. The CDLQI has been mostly used for children with AE and the mean CDLQI scores were provided in 19 studies and

provided a weighted average of 5.7 to 10.7; suggesting that overall AE has a moderate effect on QoL in children.

Data of five conditions (contained within three publications (81, 88, 92)) were not included within the meta-analysis as means and standard deviations were not given. However for these five conditions the median data fell between the ranges of estimates calculated within the meta-analysis.

Figure 6. Comparison of mean CDLQI scores by skin condition



The weighted-estimated mean CDLQI scores for acne (0 to 9.9), naevi (0 to 7.4), psoriasis (1.4 to 9.7), scabies (0.0 to 30), urticaria (0 to 18.6), vitiligo (0.4 to 10.5), and warts (0 to 7.4) were based on small numbers with wide confidence intervals and therefore the QoL effect cannot yet be fully determined.

3.4 Discussion

Two studies used the CDLQI to describe QoL in children with MC, both highlighting an overall small QoL effect from the condition when the mean CDLQI scores are provided. Both of these studies represent small numbers of children (n=7,14) and therefore it is difficult to provide a more detailed description of QoL effect from MC with strong statistical power; when the results are included within a meta-analysis it provides wide confidence intervals.

Overall the common skin conditions included within this review are shown to have had a small effect on a child's QoL. Of all of the conditions the CDLQI has been used most frequently to measure QoL for children with AE; where overall there is a moderate effect on QoL in children (CDLQI score range 5.7 to 10.7). Data included within the meta-analysis are from various study designs; in most studies (92.7%), children were recruited from dermatology outpatient clinics with only two cross-sectional studies recruiting from the community. Typically dermatologists are referred the more severe and complicated cases from primary care and so the CDLQI scores reported from secondary care may be higher than typical cases existing in the community. Studies of AE that recruited from the community reported lower CDLQI scores than studies from secondary care (males 4.7 Females 4.3 (99)), although there was a relatively low response rate (urban 35%, rural 78%) which may have been a contributing factor. This may highlight an area for future research in assessing whether the CDLQI is valid in measuring QoL in both primary, secondary, and community care scenarios. Where the dermatology life quality index (DLQI) (a QoL tool developed for use in adults aged 16 years and over) was used in adults in primary care there were comparable results to that of patients seen in secondary care (100).

Studies were excluded from the meta-analysis if data was not given of all participants at baseline before treatment or stratification into study arms. The meta-analysis therefore does not include some studies which did use the CDLQI to measure QoL and this is a limitation of the findings.

3.5 Conclusions

The CDLQI is a useful instrument to measure QoL as it allows the score to be given a severity rating and this provides a meaningful interpretation of scores. There were two published studies that provided data for children with MC, both of relatively small numbers of UK children. Where the mean CDLQI scores are produced in both studies they showed an overall small effect on QoL from the condition; meta-analysis combining the data from these two studies estimates MC has between no effect to a small effect on a child's QoL. Although the mean scores for both of these studies showed a small effect on QoL, the range of scores highlight that some children are experiencing a moderate effect on QoL (CDLQI score greater than seven) and neither study indicated what proportion of children presenting with MC are experiencing this higher disease severity. To explore symptoms of MC and QoL later in chapter seven, data of the presentation of MC symptoms are analysed by a child's CDLQI score to describe whether different presentations in symptoms are associated with a higher or lower effect on QoL, and provide a detailed description of the distribution of CDLQI scores within the cohort of children with MC.

Chapter four: Descriptive epidemiology of molluscum contagiosum: longitudinal retrospective cohort of children presenting to primary care in the UK.

4. Overview

This chapter will describe the incidence of primary care consultations for MC in children in the UK. The aims, objectives, data source, extraction and approval processes, and the analysis and statistical plans will be described. This will be followed by a summary of the results and a discussion of the key strengths and weaknesses. A comparison of these results to the published literature will be discussed in the final thesis discussion chapter (chapter eight).

4.1 Background

The two most recently published studies describing childhood MC in the UK described primary care consultations using data from 1994 to 2003 (5) and 2006 (26) respectively, and extracted from the same sentinel practice network (Weekly Returns of the Royal College of General Practitioners). The results of these studies were described in chapter two. I have not been able to identify any more recent studies of the incidence of primary care consultations for MC in the UK.

4.1.1 MC and atopic eczema (AE)

Chapter two described that AE is common in children with MC (40, 52, 56, 101, 102) and the prevalence of AE was higher in children with MC than in the general population (48). Children diagnosed with MC are more likely to have or to have had an AE diagnosis (45). Most studies that include data on both MC and AE have described cases in speciality dermatology care (56), and while these studies clearly highlighted an association in this population, there is no published data on whether children with a diagnosis of AE in primary care have a greater risk of developing MC. It is therefore important to understand whether AE presents more commonly in those with a current MC diagnosis and/or, alternatively, children who are

diagnosed with AE, a condition shown to be associated with abnormalities in immune regulation, are also more likely in the future to develop other skin conditions such as MC. Although this analysis can't describe the causes of diseases, it may highlight an association between the two conditions which may lead to further exploration of the basic science for both conditions.

4.2 Clinical Practice Research Datalink (CPRD)

Data was extracted from the UK CPRD which is a primary care database of anonymised patient records representing almost 6% of the UK population. CPRD collects routinely collected data prospectively from participating general practices in the UK and currently contains data from over four million active patients and 500 primary care practices across the UK (103). The database is maintained and managed by the NHS National Institute for Health Research (NIHR) and access to the data are available to researchers to support innovative and informative research. Data can be linked to secondary care data, diseases registries and key socio-demographic datasets. The data held within CPRD are validated and been found to be generalisable to the UK population (104).

4.2.1 CPRD Datasets

CPRD is a relational database and uses data from registered UK primary care practices. CPRD includes data relating to the individual consultation such as the date, time of the consultation, and diagnosis. Consultation data can then be linked to further tables held within the database that make up the CPRD dataset containing information about the individual patient, staff information, practice demographics, referral/s to secondary care, immunisation/s, tests and prescribed therapies. The tables can be linked by the unique patient identifier which is provided by CPRD. The patient identifier is included within each row of all data held in CPRD and the data held within CPRD is anonymised meaning individual patients cannot be identified from the data source.

Any diagnosis given during a consultation is recorded as a Read-code. CPRD data are coded using schemes and dictionaries used in the NHS such as Read and the International Classification of Diseases (ICD-10), and therapies are coded using the British National Formulary (BNF) (105).

4.2.2 Data quality

CPRD defines the quality of the data recorded by the primary care practice and also the quality of the data relating to the patient. Practices are marked as being “up-to standard” (acceptable=1 or unacceptable=0) following a quality assessment, this quality marker measures that the practice meet specified data entry quality criteria (106).

Individual patients are quality measured as being “research acceptable” (acceptable=1 or unacceptable=0), those marked as being “research acceptable” are assessed to ensure they hold a complete and valid dataset (complete data for age, gender, date of registration, and hold no data outside of normal ranges (i.e. a consultation prior to birth)).

4.3 Aims and objectives

This study aims to describe the consultation rate of children presenting to primary care with MC in the UK, the management of MC in primary care, and test the hypothesis that a history of AE increases the likelihood of a future MC consultation during childhood.

4.3.1 Primary objective

The primary objective was to describe the consultation rate for MC per 1,000 total CPRD practice population, age and sex distribution, and trend analysis of overall rates of disease presenting to general practice.

4.3.2 Secondary objectives

The secondary study objective was to examine management of MC in terms of treatments prescribed and referral to other services, and relationship to AE.

4.4 Study Design

Two studies are reported in this chapter: a retrospective longitudinal study of MC cases and an age-sex matched case-cohort study of AE cases.

4.4.1 Primary Aim (Study one - descriptive)

(A) Describe the trends in consultation rates for MC in individuals presenting to general practice.

Research objectives/questions

1. Stratified age/sex trends in consultation rates of MC by year of age.

(B) Describe the management of MC in primary care as recorded in primary care records.

Research objectives/questions

1. Describe medications prescribed or procedures administered for MC.
2. Describe referrals to secondary care following a diagnosis of MC.

4.4.2 Secondary Aim (Study two - hypothesis testing)

(C) Hypothesis: Children, aged zero to 14 years, are more likely to consult for MC during childhood if they have a previous diagnosis of AE.

Null Hypothesis: There is no association between a diagnosis of AE and a subsequent diagnosis of MC.

Research objectives/questions

1. Determine the likelihood of an MC consultation in children with a prior diagnosis of AE compared to those without a previous diagnosis of AE.
2. Determine whether prescribed treatments during an AE consultation, severity of eczema (based upon coded diagnosis marked as secondary aim), or age from AE impacts on likelihood of a future MC consultation.
3. Describe average time between onset of AE and first MC diagnosis.

4.4.3 Study Population

CPRD “research-acceptable” patients were extracted from all practices that were “up-to-standard” at the time of a diagnosis of MC and/or AE within a specific population subset.

4.5 Statistical Analysis

4.5.1 Retrospective longitudinal study of MC cases (study one)

4.5.1.1 Sample size calculation

From previous research (described in chapter two) the suggested incidence of primary care consultations for MC in the UK ranged from 15.0 to 17.2 per 1,000 for those aged zero to 14 years (5, 26), estimating an average practice will see 10 paediatric cases of MC per year. Within CPRD, and with an estimated number of primary care practices of 650, there may be 6,500 MC consultations per year in the zero to 14 population. If this figure over estimates the actual number and the true population is as much as 20% lower, the CPRD database will provide a large sample for the analysis being conducted. This would also provide a larger population than previous studies in the UK.

4.5.1.2 Analysis

The consultation rate was calculated using age-specific rates of numbers diagnosed against total population in the specified age group of CPRD. Consultation rates were produced by age and year to produce annual trends of MC. To test for seasonality of consultations, rates were produced quarterly with an ARIMA test of seasonality performed, and data presented in a correlogram to highlight seasonal variation.

4.5.1.3 Denominator

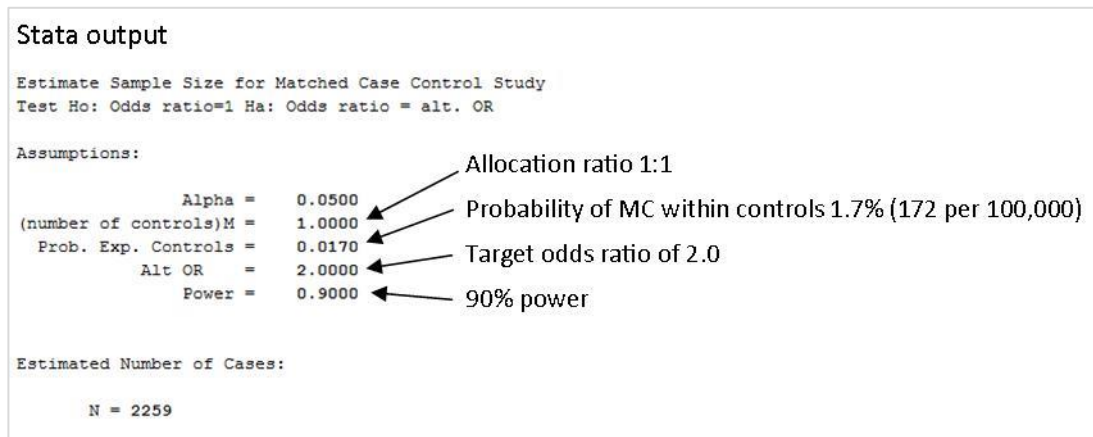
The denominator data used was the overall population of CPRD. Patients were included within the denominator dataset from practices marked “up-to standard” and if the patient was “research acceptable”.

4.5.2 Age-sex matched case-cohort study (study two)

4.5.2.1 Sample size calculation

Previous studies have been insufficient in calculating the likelihood of a child having a future MC consultation following an AE diagnosis by a GP, and this is mainly due to having no control group within their study population. Given an estimated consultation rate for MC and AE of 172 and 603 per 10,000 respectively, in order to detect a minimal OR of 2.0 with 90% power and 95% confidence it would require a minimum of 2,259 cases with AE and age-sex matched controls within each age subset. Controls for the case-cohort analysis were selected at random within age-sex strata at a ratio of 1:1. This estimate was calculated within STATA 12 using the *sampsi_mcc* command (107), the values used within this calculation and output are shown below (Figure 7).

Figure 7. Case-cohort study sample size calculation



The CPRD dataset holds over the required number of annual paediatric cases of AE, indicating that the proposed secondary analyses will be adequately powered.

4.5.2.2 Analysis

Logistic regression analysis was used to determine odds ratios for the association between 'exposure' to AE and the risk of an MC outcome. Multivariate analyses were also performed. In the multivariate models the data were adjusted for age, treatment and eczema diagnosis

(primary and secondary diagnosis, as marked on Read-codes (Table 8)). Significance was assumed at the 5% level, and 95% confidence intervals are reported.

For the purposes of reporting results of the multivariate analysis no data were reported where numbers are less than five to ensure no unintentional (deductive) disclosure arose.

4.5.2.3 Exposure

Baseline exposure to AE was defined as a 30 day AE free ‘wash-in’ period where there are no consultations for AE prior to first recorded diagnosis of MC. An AE diagnosis during the ‘primary outcome’ consultation for MC will not be classed as prior exposure.

4.5.2.4 Treatments

Treatments or no treatment for AE were categorised for covariate analysis. The severity of AE was also measured by the potency of corticosteroids prescribed as shown in Table 7 below. Consultations that involved a code for mild to moderate AE treatment and a dermatology referral were classed as having severe AE. The dermatology referral for AE needed to be 30 days prior to the MC diagnosis to ensure the referral was not for MC.

Table 7. Treatments for AE and severity

Severity	Potency of corticosteroids
Severe	Very potent or super potent (up to 600 times as potent as hydrocortisone)
	Potent (100-150 times as potent as hydrocortisone)
Moderate	Moderate (2-25 times as potent as hydrocortisone)
Mild	Mild (Hydrocortisone)

4.5.3 Analytical Software

Analysis was performed using statistical software STATA 12.

4.5.4 Missing Data

As only data from patients flagged as being of 'research-acceptable' quality were used there was no missing data for age, gender or practice. No participants were recorded as gender indeterminate.

4.5.5 Read-Codes

For MC there were two Read-codes that clinicians were able to use when diagnosing MC within CPRD, both of these were selected for extracting data. NF produced a list of AE diagnosis for extraction; less common eczema's were marked for secondary analysis. The Read-codes used for extraction of data from CPRD are shown in Table 8.

Table 8. MC and AE CPRD Read-codes

Read-code	Description	Secondary analysis
Molluscum Contagiosum		
A780000	Molluscum contagiosum with eyelid involvement	-
A780.00	Molluscum contagiosum	-
Atopic Eczema		
8HTu.00	Referral to eczema clinic	
A540.00	Eczema herpeticum - Kaposi's varicelliform eruption	
F4D3000	Eczematous eyelid dermatitis	
M07y.11	Pustular eczema	Secondary
M102.11	Pustular eczema	Secondary
M111.00	Atopic dermatitis/eczema	
M112.00	Infantile eczema	
M113.00	Flexural eczema	
M114.00	Allergic (intrinsic) eczema	
M119.00	Discoid eczema	
M11A.00	Asteatotic eczema	Secondary
M12z100	Eczema NOS	
M12z111	Discoid eczema	
M12z200	Infected eczema	Secondary
M12z300	Hand eczema	Secondary
M12z400	Erythrodermic eczema	Secondary
Myu2.00	Dermatitis and eczema	Secondary
Myu2200	Exacerbation of eczema	
M11..00	Atopic dermatitis and related conditions	Secondary
M11z.00	Atopic dermatitis NOS	
M252100	Pompholyx unspecified	Secondary
M12z000	Dermatitis NOS	Secondary

4.6 Approvals

The study protocol was reviewed by the Independent Scientific Research Committee (ISAC) for the UK Medicines and Healthcare Products Regulatory Agency (MHRA) database research. Approval was granted on 17th March 2014 for CPRD data to be extracted and used for the purposes defined within this chapter and within the study protocol [ISAC Ref: 14_058R]. A copy of the ISAC approval letter relating to this research can be found in appendix 5.4.

4.7 Data extraction and cleaning

4.7.1 Data extraction

Data were extracted from the CPRD database through the Cardiff University licence providing access directly to the data source. The data was requested from the 'Pharmatelligence' team⁵ within the Institute of Primary Care and Public Health by NF and provided to myself on 19th May 2014 in a series of linked data tables in text format. Data was only provided from "up to standard practices" and therefore each data field held complete data and was ranked by CPRD as having a high standard of accuracy.

4.7.2 Data cleaning

Data were provided in nine text files which each held the unique identifiers for a consultation of patient ID and event date. All MC and AE consultations for the period 2004-13 were provided in a master file that contained information relating to the consultation, patient, and practice.

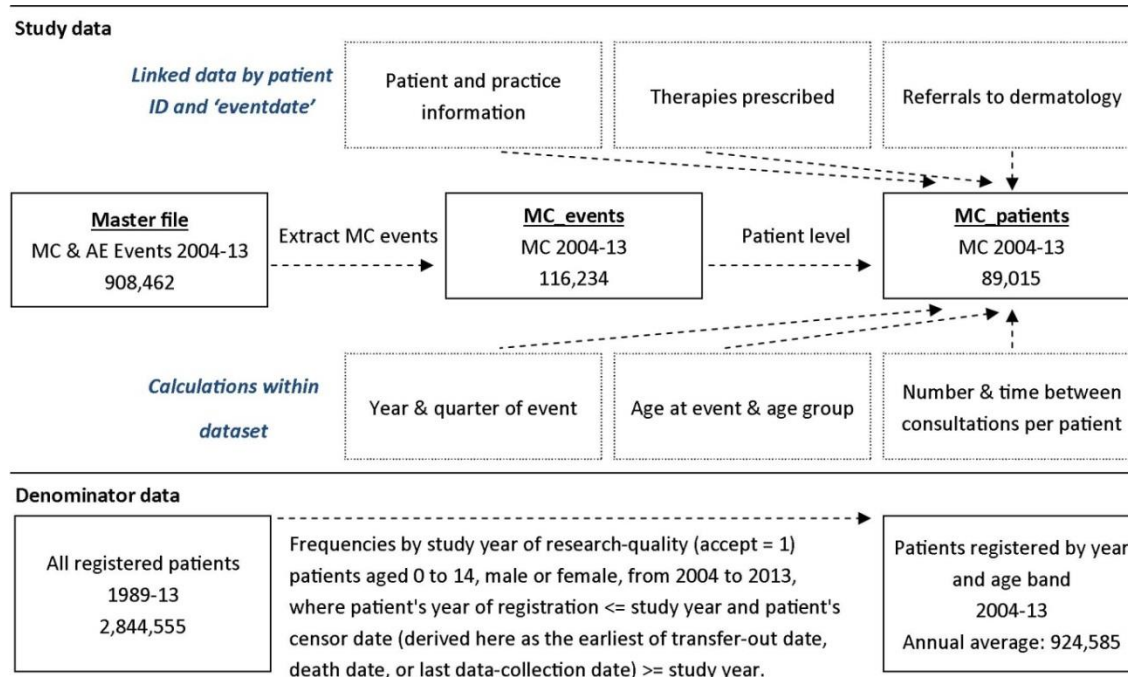
4.7.3 MC dataset (study one)

Data relating to MC consultations identified by the appropriate Read-code were extracted from the master file to prepare the dataset for analysis. Where a patient had multiple consultations for MC during the time period, the data for each consultation was grouped within a single row of data (Figure 8). Data relating to referrals to dermatology and therapies

⁵ Pharmatelligence is a private enterprise located and aligned with Cardiff University.

prescribed were merged into the dataset using the identifiers of patient ID and event-date. Within the dataset new fields were created to describe the time between consultations, number of consultations, age at event, and the month, quarter, and year of event.

Figure 8. Data cleaning and preparation for analysis (MC consultations 2003-14)



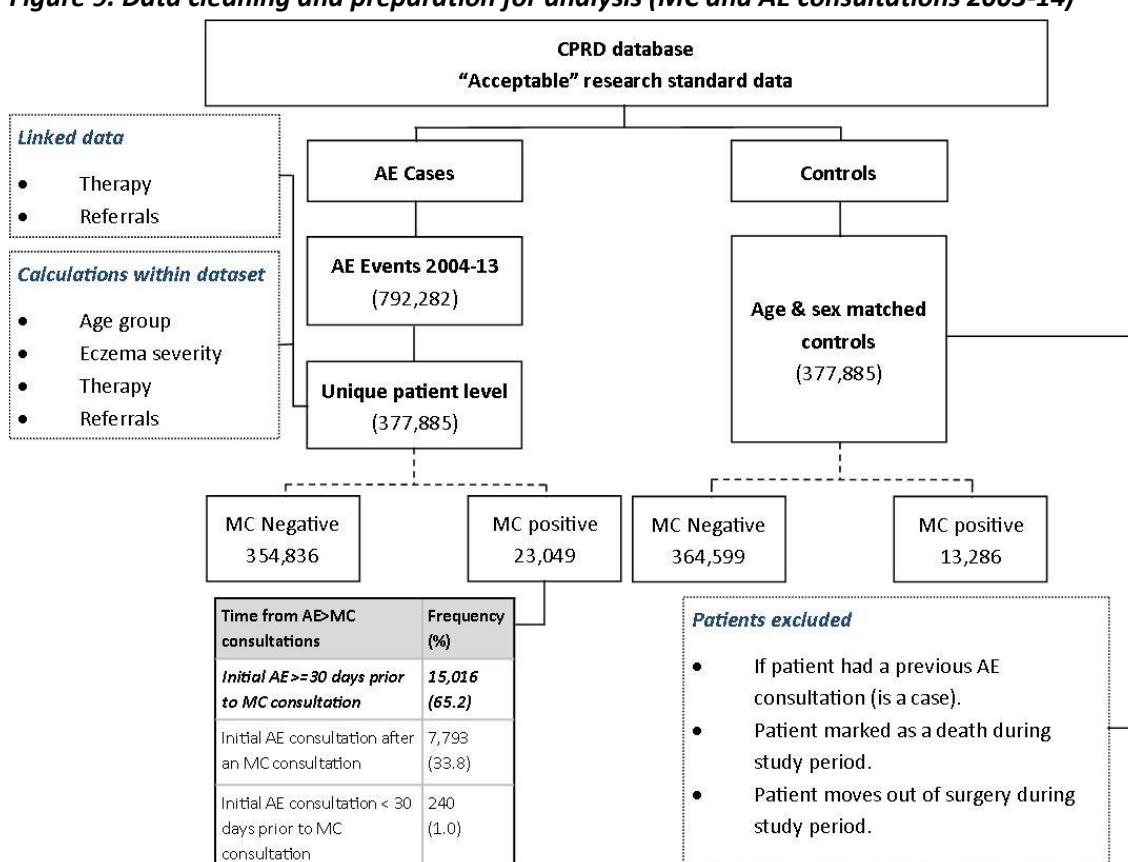
4.7.4 MC and AE dataset (study two)

Data for all AE consultations during 2004-13 were extracted from the master dataset. Consultations per patient were joined to produce a wide database where each row was a uniquely identifiable patient (Figure 9). The total number of consultations per patient for an AE Read-code was calculated and included on the row, as was the date of the first AE consultation for that patient. Data relating to referrals and therapies were joined based upon patient ID and event-date of the consultation; only referrals coded for 'dermatology speciality' were included in the final dataset. Therapies for corticosteroids were marked by severity based upon their BNF chapter classification of potency (as per Table 7). The data were merged with the 'MC Master' file (all consultations 2004-13) by patient ID. The dates between the first AE and initial MC consultations were calculated and coded for the purposes of analysis.

An age (year of birth) and sex matched control group was extracted from the CPRD registered population. Patients who ‘transferred out of practice’ or died during the study period were removed. Children who had an AE diagnosis or also featured within the cases group were extracted from the population pool before the controls were selected randomly.

The control group was merged with the ‘MC master’ database to identify if any patients consulted for MC during 2003-14.

Figure 9. Data cleaning and preparation for analysis (MC and AE consultations 2003-14)



4.8 Results

4.8.1 Retrospective longitudinal study of MC cases (study one)

During the period 2004-13 there were 116,234 consultations for MC within the CPRD database that met the inclusion criteria for 89,015 unique individuals. The initial consultation that a patient had for MC is used within the analysis of the data in this chapter.

Two Read-codes for MC are available: one for, 'Molluscum contagiosum' and one for, 'Molluscum contagiosum with eyelid involvement'. Almost all cases identified in CPRD had been coded with the first Read code, 38 cases (0.04%) used the 'eyelid involvement' code (Table 9).

Table 9. Count and percentage of MC consultations aged 0 to 14 years, 2004-13 by Read-code.

Read-code	Description	Events	%
A780.00	Molluscum contagiosum	88,977	99.96
A780000	Molluscum contagiosum with eyelid involvement	38	0.04
<i>Total</i>		<i>89,015</i>	<i>100</i>

4.8.1.1 Patient demographics

Of the 89,015 unique patient consultations, 44,995 were for males, representing 50.6% of the total study population (Table 10).

Table 10. Count and percentage of patient gender aged 0 to 14 years, 2004-13

Gender	Events	%
Male	44,995	50.55
Female	44,020	49.45
<i>Total</i>	<i>89,015</i>	<i>100</i>

4.8.1.2 Consultation rates for MC

Gender

There was little difference in mean consultation rates between males and females in children aged zero to 14 years over the 10 year period (Table 11).

Table 11. Consultation rate per 1,000 registered population 2004-13 aged 0 to 14 years by gender

Gender	Events	Pop	Rate per 1,000	LCI	UCI
Male	44,995	4,739,203	9.5	9.4	9.6
Female	44,020	4,506,644	9.8	9.7	9.9
<i>Total</i>	<i>89,015</i>	<i>9,245,847</i>	<i>9.6</i>	<i>9.6</i>	<i>9.7</i>

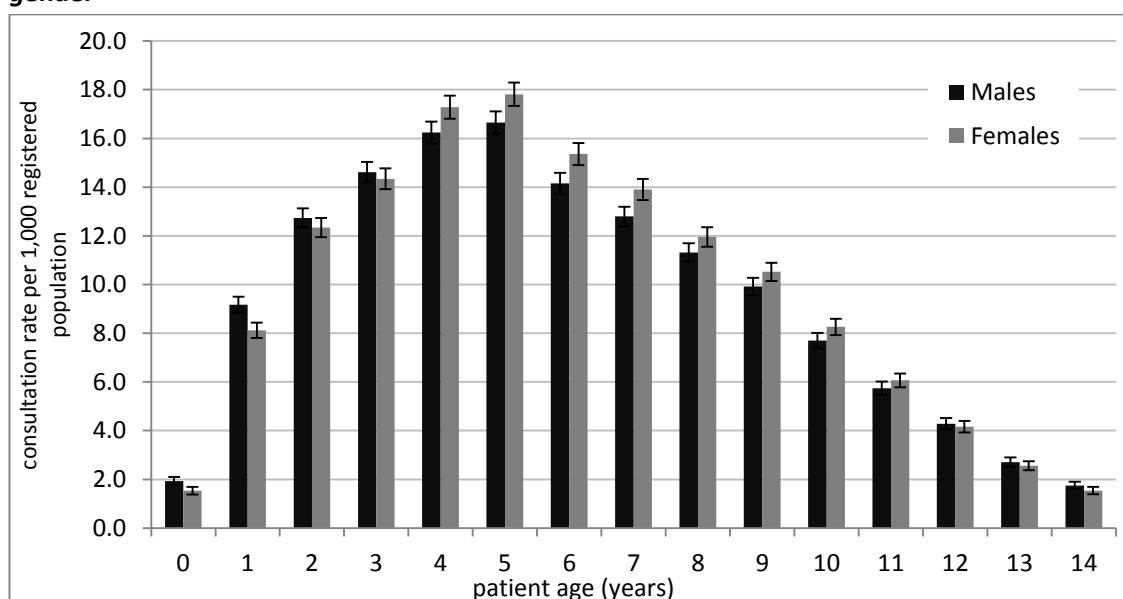
Age

The highest consultation rates were in children aged four and five years for both males and females (Table 12). Figure 10 shows that MC consultations rates are more common in younger children aged less than 10 years. The main peak in consultation rates is seen in children aged three to seven years.

Table 12. Consultation rate per 1,000 registered population, 2004-13, by age(year) and gender

Age	Events		Population		Consultation rate per 1,000					
	M	F	M	F	M	LCI	UCI	F	LCI	UCI
0	547	411	282,744	268,564	1.9	1.8	2.1	1.5	1.4	1.7
1	3,090	2,603	337,101	320,516	9.2	8.8	9.5	8.1	7.8	8.4
2	4,236	3,906	332,492	316,642	12.7	12.4	13.1	12.3	12.0	12.7
3	4,768	4,457	326,299	310,812	14.6	14.2	15.0	14.3	13.9	14.8
4	5,202	5,271	320,142	304,949	16.2	15.8	16.7	17.3	16.8	17.8
5	5,235	5,336	314,413	299,534	16.7	16.2	17.1	17.8	17.3	18.3
6	4,392	4,544	310,215	295,805	14.2	13.7	14.6	15.4	14.9	15.8
7	3,950	4,092	308,714	294,364	12.8	12.4	13.2	13.9	13.5	14.3
8	3,497	3,520	309,071	294,392	11.3	10.9	11.7	12.0	11.6	12.4
9	3,077	3,108	310,205	295,437	9.9	9.6	10.3	10.5	10.2	10.9
10	2,398	2,452	311,589	296,797	7.7	7.4	8.0	8.3	7.9	8.6
11	1,807	1,817	314,791	299,657	5.7	5.5	6.0	6.1	5.8	6.3
12	1,363	1,258	318,224	301,966	4.3	4.1	4.5	4.2	3.9	4.4
13	870	777	321,068	303,422	2.7	2.5	2.9	2.6	2.4	2.7
14	563	468	322,135	303,787	1.7	1.6	1.9	1.5	1.4	1.7
Total	44,995	44,020	4,739,203	4,506,644	9.5	9.4	9.6	9.8	9.7	9.9

Figure 10. Consultation rate per 1,000 registered population, 2004-13, by age (year) and gender



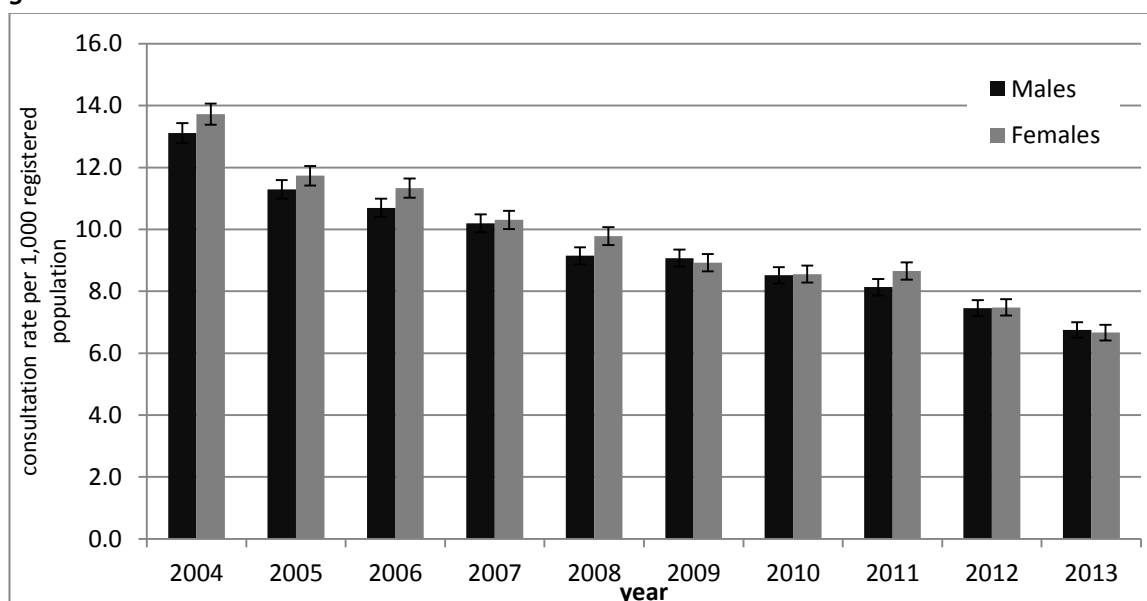
Year

Consultations for MC have been steadily declining from 2004 to 2013 (Figure 11). Rates for males have declined by 48.1% over the 10 year period, and for females the decline is similar (51.1%) (Table 13). During the period 2004-2011 females had a higher consultation rate for MC than males, in 2012 the rates between genders were equal, and in 2013 males had a marginally higher rate than females (Figure 11).

Table 13. Consultation rate per 1,000 registered population aged 0 to 14 years, by year and gender

Year	Events		Population		Consultation rate per 1,000					
	M	F	M	F	M	LCI	UCI	F	LCI	UCI
2004	6,415	6,302	489,203	459,188	13.1	12.8	13.4	13.7	13.4	14.1
2005	5,504	5,395	487,412	459,831	11.3	11.0	11.6	11.7	11.4	12.0
2006	5,256	5,280	491,478	465,970	10.7	10.4	11.0	11.3	11.0	11.6
2007	4,981	4,788	488,420	464,567	10.2	9.9	10.5	10.3	10.0	10.6
2008	4,407	4,493	481,759	459,298	9.1	8.9	9.4	9.8	9.5	10.1
2009	4,328	4,069	477,245	455,940	9.1	8.8	9.3	8.9	8.7	9.2
2010	4,037	3,867	474,016	452,026	8.5	8.3	8.8	8.6	8.3	8.8
2011	3,758	3,820	462,035	441,239	8.1	7.9	8.4	8.7	8.4	8.9
2012	3,368	3,231	451,934	432,115	7.5	7.2	7.7	7.5	7.2	7.7
2013	2,941	2,775	435,701	416,470	6.8	6.5	7.0	6.7	6.4	6.9
Total	44,995	44,020	4,739,203	4,506,644	9.5	9.4	9.6	9.8	9.7	9.9

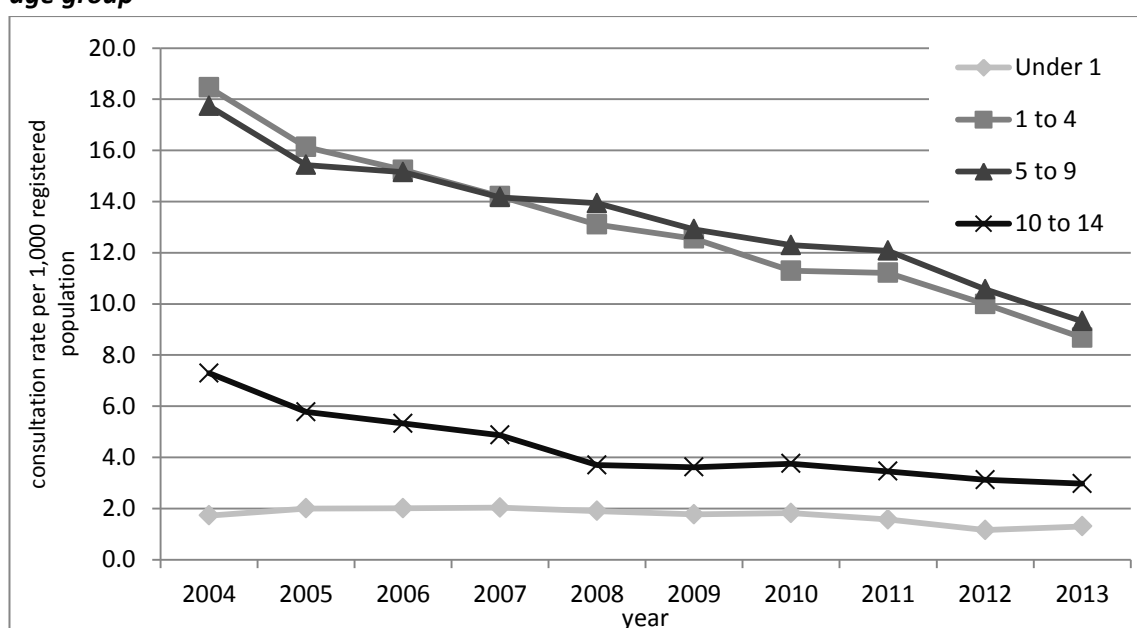
Figure 11. Consultation rate per 1,000 registered population aged 0 to 14 years, by year and gender.



4.8.1.3 Trends

Overall for males and females consultations for MC decreased by 50.5%, decreases were highest for children within the one to four and five to nine age groups between 2004-13 (Figure 12). Rates for children aged 10 to 14 years declined between 2004 to 2008 and remained constant from 2008 to 2013. There was little variation in the rate of consultations for children aged less than one year for the 10 year period.

Figure 12. Consultation rate per 1,000 registered population, males and females, by year and age group



4.8.1.4 Consultations per patient

Most patients consulting for MC did so once (77.3%), 17.6% had two consultations for MC, and a small proportion (~5%) presented on three or more occasions (Table 14).

Table 14. Number of consultations per patient during period 2004-13.

Number of consultations	Frequency	%	Cumulative %
1	68,820	77.3	77.3
2	15,662	17.6	94.9
3	3,544	4.0	98.9
4	685	0.8	99.7
5 or more	304	0.3	100.0
Range	1	to	8
Median	1	Q_1 to Q_3	1 to 1

The time between MC consultations varied, 89.5% of patients who did consult more than once for MC (n = 20,195) did so within one year of their initial consultation for MC (Table 15).

Table 15. Time between initial MC consultation and final consultation between 2004-13

Time between consultations	Frequency	%
Less than 1 year	18,082	89.54
Over 1 year	2,113	10.46
<i>Total</i>	<i>20,195</i>	<i>100</i>

4.8.1.5 Patient episodes of MC

Where data are presented as patient episodes, assuming a singular episode of MC as one or more MC consultations within 180 days, 90.4% of children had one episode, 9.3% two, and 0.3% three or more.

4.8.1.6 Referral to secondary care

There were 733 (0.8% of total children) referrals to a secondary care dermatology department in children during an MC consultation (Table 16). The greatest referral rate was in those aged 10 to 14 years (9.9 per 1,000 MC consultations). The rate in referrals from 2004 to 2013 reduced significantly by 74.4% during the 10 year period (Table 17). In 2004 there were 174 referrals to a dermatologist; this had reduced to 20 referrals in 2013.

Table 16. Referral's to secondary care dermatologist per 1,000 MC consultations, males and females, 2004-13, by age group

Age Group	Referrals	Population	Referral rate per 1,000 MC consultations
Under 1	6	958	6.3
1 to 4	280	33,533	8.3
5 to 9	310	40,751	7.6
10 to 14	137	13,773	9.9
<i>Total</i>	<i>733</i>	<i>89,015</i>	<i>8.2</i>

Table 17. Referral's to secondary care dermatologist per 1,000 MC consultations aged 0 to 14 years, males and females, by year

Year	Referrals	Population	Referral rate per 1,000 MC consultations
2004	174	12,717	13.7
2005	114	10,899	10.5
2006	75	10,536	7.1
2007	78	9,769	8.0
2008	51	8,900	5.7
2009	55	8,397	6.5
2010	70	7,904	8.9
2011	44	7,578	5.8
2012	52	6,599	7.9
2013	20	5,716	3.5
<i>Total</i>	<i>733</i>	<i>89,015</i>	<i>8.2</i>

Of the patients who were referred to a secondary care dermatologist, 73.4% had consulted two or more times to their GP with MC (Table 18).

Table 18. Referrals to dermatology and single or multiple consultations for MC

Consult 2 or more times for MC	Frequency	%
Y	538	73.4
N	195	26.6
<i>Total</i>	<i>733</i>	<i>100</i>

4.8.1.7 Prescribed medications

46.6% of patients received a treatment during a consultation for MC during either their first or subsequent consultation (if there were multiple consultations) (Table 19).

Table 19. Treatment prescribed during a patient's consultation for MC

Did patient receive a treatment coded for MC during a consultation?	Event	Percent
Yes	41,489	46.6
No	47,526	53.4
<i>Total</i>	<i>89,015</i>	<i>100</i>

Of the 41,489 patients who were prescribed a treatment coded for an MC diagnosis, a total of 71,404 treatments were prescribed. The average number of items per patient was 1.7. Treatments prescribed in over 1% of these cases are listed in Table 20 by BNF sub-section headings.

Table 20. Treatments coded for diagnosis of MC (where prescribed in over 1% of cases)

BNF sub-section heading	Freq.	%
Emollient & Barrier Preparations	14,645	20.5
Topical Corticosteroids	14,496	20.3
Anti-Infective Skin Preparations	13,075	18.3
Antibacterial Drugs	10,647	14.9
Antihistamines, Hyposensitisation & Allergic Emergencies	3,097	4.3
Preparations For Warts And Calluses	1,727	2.4
Bronchodilators	1,635	2.3
Skin Cleansers, Antiseptics & Wound prep	1,412	2.0
Analgesics	1,129	1.6
Anti-Infective Eye Preparations	938	1.3
Corticosteroids	829	1.2
Top Local Anaesthetics & Antipruritic	750	1.1

4.8.1.8 Time series of consultations

Consultation rates for MC by quarter are shown in Figure 13, and although there are decreasing consultation rates overall for the period 2004 to 2013, seasonal peaks can be seen during the second quarters of each year from 2004 to 2011. During 2012 there was little variation in consultation rates between each quarter. Consultation rates were lowest during the fourth quarter of each year.

Where the data are plotted in a correlogram (Figure 14) a pattern emerges whereby each fourth data point peaks, showing a stronger correlation than the previous three, thus implying that there is a seasonal relationship in the rates of consultations for MC within the dataset. Overall there is negative correlation shown in the correlogram representing the declining consultation rates.

To explore the strength in relationship between the rate of consultations of MC and seasonality, an ARMIA test of regression was performed. The test results show a strong relationship between each data point and the average of those previous data points combined (AR[1]) ($\alpha=0.95$ $p<0.05$). The moving average between each fourth point (to highlight quarterly data) (MA[4]) also shows a very strong relationship ($\alpha=0.61$ $p<0.05$) highlighting a seasonal pattern in MC consultations.

Figure 13. Consultation rate per 1,000 registered population, males and females, by quarter 2004-13

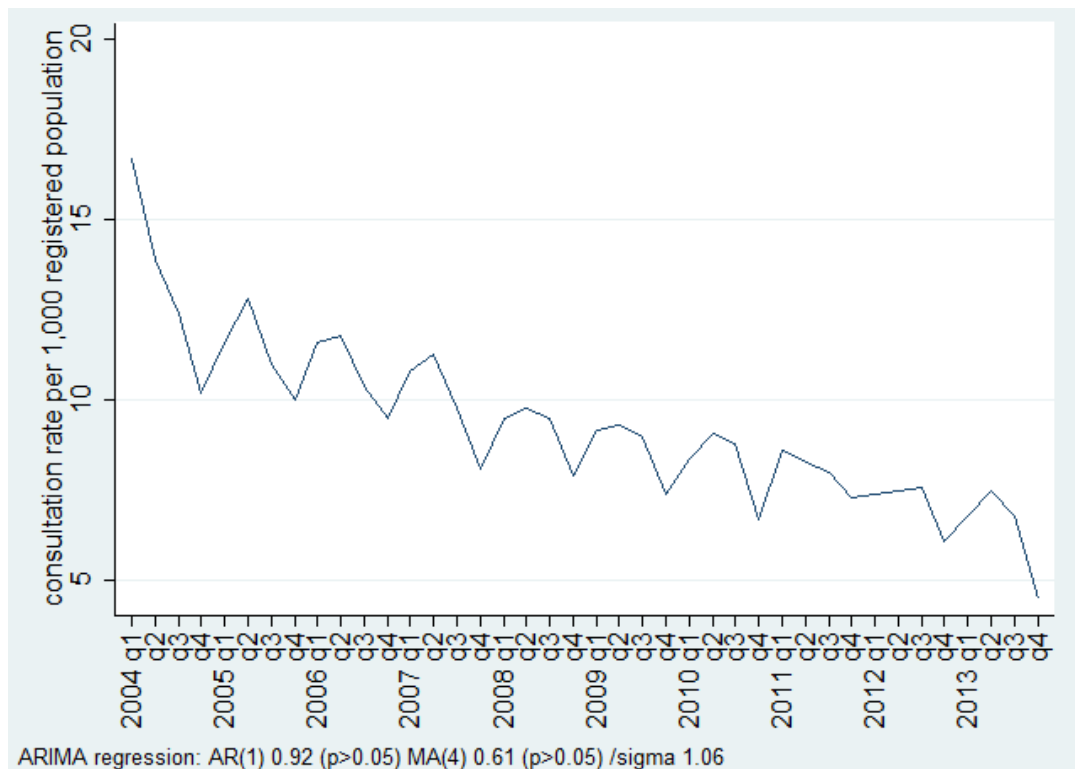
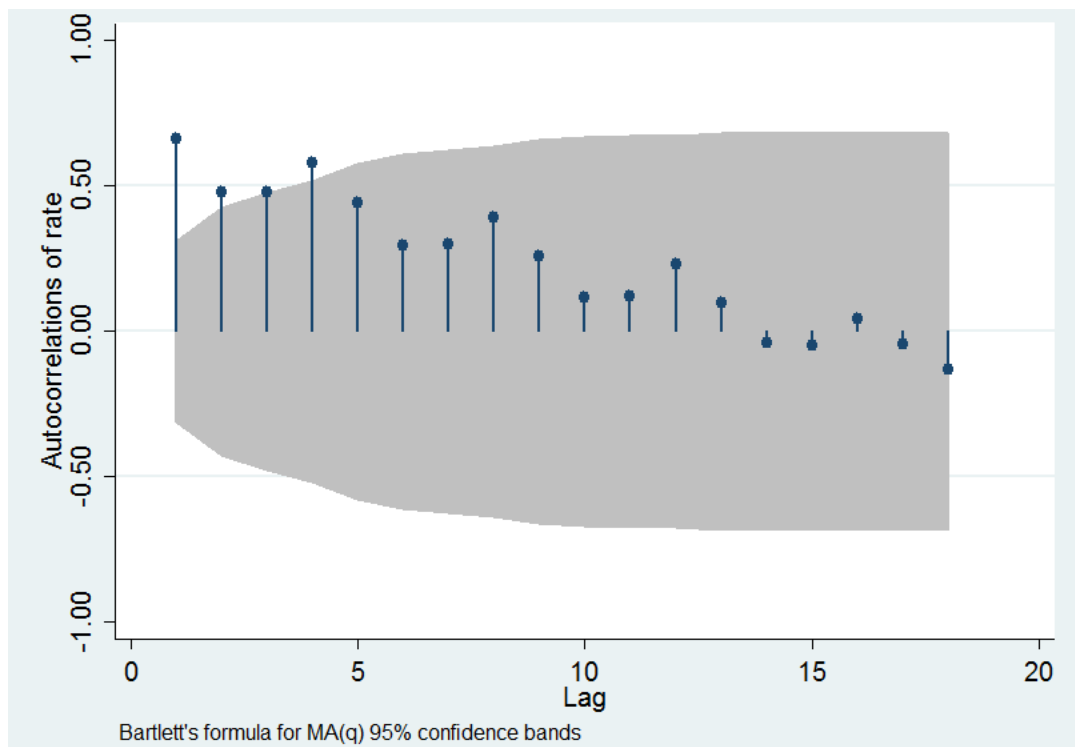


Figure 14. Correlogram of consultation rates for MC in relationship to point zero by quarter 2004-13



4.8.2 Estimation of actual patients presenting to primary care

The most recent practice populations published for England and Wales by ONS in 2011 (108) can be used to model the number of MC consultations a hypothetical practice of 6,000 patients may have during a year. This hypothetical practice accepts the overall population structure of practices in England and Wales, providing a population structure of: children aged one year and under (1.3% (of total population), n=77.9), one to four years (5%, n=298.8) five to nine years (5.6%, n=334.7) and 10 to 14 years (5.7%, n=343.8). Where the consultation rates, by age band, calculated in this chapter are applied to this model, it provides an estimate that an average practice would experience 11 recorded consultations for MC per year in children aged one to 14 years. This calculation can be compared to estimates produced in other publications.

4.8.3 Age-sex matched case-cohort study (study two)

During the period 2004-13 there were 792,282 consultations identified with an AE Read-code, where data are reformatted from long to wide format, and consultations were merged into unique patient identifiable rows there were a total 377,885 patients consulting for AE during the 10 year period.

In summary, 58.9% of children consulted once for AE (Table 21), 19.4% did so twice, and one patient consulted 105 times during the 10 year period. The median (Q_1, Q_3) consultations per patients with AE was 1 (1,3).

Table 21. Number of consultations for AE per patient during period 2004-13

Number of consultations	Frequency	Percent	
1	222,710	58.9	
3	73,270	19.4	
4	32,523	8.6	
5 or more	49,382	13.1	
Range	1	to	105
Median	1	Q_1 to Q_3	1 to 3

In children who consulted for both AE and MC around three quarters (65.2%) of initial AE consultations were over 30 days prior to their first consultation for MC (Table 22). 1.0% of cases consulted within 30 days of their first MC diagnosis, and 33.8% of children consulted for AE on the same date or after an MC consultation.

Table 22. Time between AE and MC consultation in cases of AE who also consulted for MC.

Time from AE>MC consultations	Frequency	Percent
Initial AE >=30 days prior to MC consultation	15,016	65.2
Initial AE consultation during or after an MC consultation	7,793	33.8
Initial AE consultation < 30 to 1 day prior to MC consultation	240	1.0
<i>Total children who consulted for AE and MC</i>	<i>23,049</i>	<i>100</i>

Children diagnosed with AE were more likely to have a future MC consultation during childhood than controls (OR 1.13 (95% CI 1.10 to 1.16) $P<0.005$) (Table 23).

Table 23. Odds ratio (OR) of MC consultation in patients with previous AE diagnosis

Cases		Controls		OR	95% CI	P
No MC	MC	No MC	MC			
362,869	15,016	364,599	13,289	1.13	1.11 to 1.16	<0.005

In the multivariate model, odds ratios were adjusted for the following confounders; corticosteroid potency prior to MC diagnosis, age at initial AE consultation and primary or secondary AE diagnosis (Table 24). Corticosteroid potency and type of AE diagnosis did not influence the likelihood of an MC diagnosis. However, younger children were more likely to have an MC consultation than older children aged 10 to 14 years (OR 1.37 (95% CI 1.32 to 1.42) $P<0.005$).

Corticosteroid therapy during an AE diagnosis was prescribed in 102,838 children before an MC diagnosis (>30 days) or where there was no future MC consultation documented. In 97.3% of cases the potency was mild, 0.1% moderate, and 2.6% potent or very potent. There was no significant difference in the risk of developing MC between children prescribed various potencies of corticosteroids.

Table 24. Unadjusted odds ratios (OR) for future MC consultation in children with AE

a) Corticosteroids potency				
	Corticosteroid strength	OR	95% CI	P
	Mild	Ref		
	Moderate	0.37	0.10 to 1.50	0.16
	Potent or very potent	0.88	0.73 to 1.06	0.17
b) Age at initial AE diagnosis				
	Age group (years)	OR	95% CI	P
	Under 1	Ref		
	1 to 4	1.37	1.32 to 1.42	<0.005
	5 to 9	1.04	0.99 to 1.10	0.07
	10 to 14	0.25	0.23 to 0.27	<0.005
c) AE diagnosis (as per Table 8)				
	Analysis	OR	95% CI	P
	Primary AE diagnosis	Ref		
	Secondary AE diagnosis	0.89	0.83 to 0.94	<0.005

4.9 Discussion

Data were extracted from CPRD, a large primary care database containing over four million active patients in the UK for the period 2004 to 2013. In total 89,015 children aged zero to 14 years presented to their GP and were diagnosed with MC on one or more occasions. The consultations rate for MC in children for males was 9.5 per 1,000 (95% CI 9.4 to 9.6) and females 9.8 per 10,000 (95% CI 9.7 to 9.9). The greatest rate for both genders is for children aged two to seven years (12.3 to 17.8 per 1,000). Children aged zero years, and aged 13 years and over had the lowest rate of consultations (less than 3 per 1,000). There are no significant differences in consulting between genders.

The rate of consultations in primary care for children diagnosed with MC by their primary care doctor declined by 50.0% during the 10 year period (48.1% in males, 51.1% females). The greatest reduction in the rate of consultations was in those aged one to four and five to nine years. The consultation rate in children aged under one year remained consistently low for the 10 year period.

The data highlights seasonal trends of consultations for MC, showing a peak during the second quarter of each year (April to June). Most children with MC presented to their GP once

(77.3%), and 17.6% had two visits relating to MC; of those who consulted more than once 90% were within one year of the initial MC consultation. Very few children were referred to secondary care (0.8% of all patients), and this reduced by 74.4% from 2004 to 2013 representing 20 referrals in total during 2013. Although a sharp reduction in consultations is shown, this data represents the current clinical management of MC in the UK that the condition should be managed by primary care doctors.

Under half of children were prescribed a medication when presenting with MC (46.6%), and the two most common prescriptions were for emollient and barrier preparations (20.5%), and topical corticosteroids (20.3%). 14.9% of children were prescribed antibacterial drugs (antibiotics) and this may suggest cases where the lesions or surrounding areas had become infected.

The study explored the associations between MC and AE, hypothesising that an AE consultation increases the likelihood of a future MC diagnosis. The results of an age-sex matched case-cohort study showed there was an increased likelihood of a child being diagnosed with MC following a previous AE diagnosis (where consultation was 30 days or more prior to initial MC consultation) (OR 1.37 (95% CI 1.32 to 1.42) $P < 0.005$). Therefore the hypothesis proposed earlier in this chapter was accepted. Younger children, aged one to four years, were more likely to have a future MC consultation if they had previously been diagnosed with AE compared to the older aged children.

The results of this chapter will be discussed in relation to those in the other studies of this thesis and other published research within the final discussion chapter of this thesis (chapter eight).

4.10 Limitations

Routinely collected datasets in primary care were designed for clinical practice and not for research. However, these datasets have become a valuable data source for research and are subject to limitations, these limitations are described within this section.

4.10.1 Potential limitations of data

As with all studies reporting the incidence of a condition using routinely collected data, this is subject to coding problems and under-ascertainment (57-59, 61-64). The most fundamental element of using data collected from primary care databases retrospectively is the reliance and assumption that the diagnoses and other data held are accurate and that the most appropriate Read-codes are used (109). For MC there are only two Read-codes available for the diagnosis and this limits errors of an incorrect diagnosis being entered for MC. Both of these Read-codes were used for data extraction in this thesis. The data extracted from CPRD for the purposes of analysis was limited to include only that marked as “up to standard”; therefore ensuring that the data extracted from CPRD is from gold standard practices by CPRD definition.

A significant limitation of the numerator data are that clinicians can also provide data about the consultation as ‘free text’. ‘Free text’ data are not coded or freely available for analysis. The ‘free text’ data are extracted and held within CPRD but accessing this data incurs substantial additional charges due to the additional steps required to ensure no potentially patient identifiable information is disclosed. The potential charges that this data extraction would have incurred meant it was not feasible for my research/this thesis. A diagnosis such as MC that will often accompany another diagnosis during a consultation, and may be considered a trivial condition by some clinicians, could be entered within the ‘free text’ area and therefore will not be included within the dataset. A ‘free text’ entry for MC may be more apparent in cases where there are no prescribed medications.

Previous studies have described regional variation in the incidence of MC (43-45), however due to the limitations of the CPRD database we were unable to explore if there were any regional variation in the incidence of primary care consultations for MC in the UK.

4.10.2 Assumptions of the dataset

The analysis performed within this chapter is limited by the assumption that the data extracted was correct and that the numerator and denominator used for the analysis will not under or over report incidence of MC. The numerator and denominator data were extracted by an experienced research analyst, and this should limit errors in the data extraction process. The data held within CPRD represents five million patients and data within CPRD are validated and found to be generalisable to the UK population (104, 110, 111). Our sample of primary care centres does not provide us with the true number of consultations for MC in the UK, however, by applying statistical techniques to the dataset it provides the range in which we believe the true estimates of the incidence of MC consultations lie (within 95% confidence). The data analysis described consultations for MC and is unable to establish the true prevalence of MC cases in the community. It can be assumed that the true prevalence of MC in the UK may be higher than the incidence rates presented when those who may be successfully managing the condition at home (and do not consult to a GP) are included.

It is also important to note that as an observational study the analysis represented in this chapter does not determine causal relationships but describes statistical associations within the data. Although observational studies do not categorically identify 'cause and effect' they are important, by identifying associations between patients characteristics, behaviours and outcomes they provide evidence of the etiology of disease and can lead to further research to explore this further.

4.11 **Conclusions**

Routinely collected data from UK primary care centres was extracted to describe the rate of MC consultations in children. The incidence of consultations were greatest for children aged three to seven years and have reduced by 50% since 2004 to 2013. The presence of MC is often accompanied by AE and children who have a history of AE are more likely to have a future MC consultation.

The result presented in this chapter are discussed in the context of other published literature in the final discussion chapter of this thesis (chapter eight).

Chapter five: Development of a parental molluscum contagiosum diagnostic tool (MCDTP)

The design outline of the MCDTP was presented at the International Investigative Dermatology conference 2013 and the abstract was published within the supplementary publication in the *Journal of Investigative Dermatology*. The published abstract can be found in Appendix 1.4.

5. Overview

This chapter will describe the process of developing the MC self-diagnostic tool for parents. Outlining the processes used for the development, the characteristics of a good disease definition for epidemiological research and initial planning phase will be explained.

The assessment of the extent to which the instrument is valid, and processes used for this assessment in GP practices are described in chapter six.

5.1 Theoretical Perspective

Some epidemiologists have argued that the standardisation of a disease definition as being of paramount importance for studies if epidemiological comparisons are to be made, and that it may even be better to have a slightly deficient definition of known validity than a definition proposed by experts of unknown validity (112).

Epidemiologists have tried to identify the elements of a good disease definition. These have been summarised nicely by Williams (1997) (112) who suggests a good epidemiological disease definition should be formed with careful consideration and that it will conform to the following areas:

- 1) Valid (sensitivity and specificity)
- 2) Repeatable (between and within observer)
- 3) Acceptable to the population
- 4) Rapid and easy to perform by field workers

- 5) Coherent with prevailing clinical concepts
- 6) A reflection of some degree of morbidity
- 7) Comprehensive in its applications
- 8) Comparable with other studies

Where conditions are characterised by their distinct features, parents when supported with a diagnostic aid, can complete self-administered questionnaires to mark the presence of the condition (113). Parental diagnosis of conditions have provided reasonably adequate answers regarding the current occurrence of clear-cut symptoms (114). Self-diagnosis, or parental diagnosis for minors, of conditions for the purposes of epidemiological research can be beneficial as an alternative to a physicians' diagnosis, and for the purposes of assessment for an epidemiological study, an examination by a medical practitioner can be expensive and impractical (115). Patient administered questionnaires also have many benefits; being easy to administer, convenient for the patient, and require less funding and personal resources than many alternative methods (116). It is essential, however, that assumptions and recruitment into epidemiological studies are only given where the validity and limitations of the tool measuring responses are known (117).

Recent epidemiological cross-sectional studies examining children for a diagnosis of MC have used various methods; six studies confirmed a diagnosis following a clinical examination (21, 25, 36-39), one relied upon parents to recall a diagnosis (40), and one did not state how a diagnosis was confirmed (24). Currently no tool with known validity exists to allow parents to self-diagnose MC in their children. The aim of this chapter is to develop a tool for this purpose.

In dermatology, tools using medical illustrations and text to help patients self-diagnose other skin conditions have been evaluated. The Psoriasis Screening Tool (PST) was designed with the purpose of being used in epidemiological studies and was found to have a high sensitivity and specificity of 96.4% (95% CI 93.2 to 98.0) and 97.3% (95% CI 94.1 to 98.9) respectively when compared to a dermatologist diagnosis (115). 222 adults (aged 18+) completed the PST and

they were equally distributed between a psoriasis and non-psoriasis group. Participants were recruited from a North American dermatology clinic and therefore may be familiar with examining their skin condition prior to attending the centre to distinguish the key diagnostic elements, this may limit the future application of the PST to dermatology centres or require further testing if it were to be used in the community. A study exploring the accuracy of self-diagnosis of a variety of skin lesions through the use of 12 lesion images and matching them to a correct diagnosis using diagnostic support software found that non-clinicians (n=23) correctly diagnosed 96% of lesions (n=231/240). The software image library contained 80 images from five diagnostic classifications that are typical referred to dermatologists in the UK and participants were guided through levels in the software before confirming a final diagnosis. All images were taken by a medical photographer and the participants were not diagnosing their own skin conditions. When this is compared to medical students (n=27) who had recently completed a two week dermatology attachment and did not use diagnostic support software, their diagnostic accuracy is considerably lower 51% (n=160/312) (118).

Using a standardised questionnaire to measure the presence of skin disease in both a health seeking (n=99) and non-health seeking population (n=98) of Norwegian adults (aged 30+ years), it provided a best sensitivity and specificity of 61% specificity 69% compared to a dermatologist (119). This instrument guided participants through 10 questions that were developed to measure presence of common skin diseases in the population and did not identify specific conditions. Although it has a relatively low accuracy in measuring the presence of a skin condition, the authors noted further development was required before use in a large epidemiological study. This tool could be used to measure the burden of skin conditions, but without an accompanying clinical diagnosis this tool cannot diagnose a specific condition.

By using medical illustrations to aid parents in making a diagnosis of a dermatological condition this can increase the sensitivity of a diagnosis (115), therefore medical images

combined with a textual description will form the basis of the MC parental diagnostic tool that will be used later in this thesis as a recruitment tool.

Through this chapter, I will use the eight components described by Williams to develop a good epidemiological disease definition of MC in children using images and text, summarising in the discussion how each of the components have been fulfilled.

5.2 Development of a draft diagnostic tool

5.2.1 Initial Planning and Development

The initial planning and development of the MCDTP was discussed during project planning meetings attended by NF, JG, VP⁶, SW (patient representative) and I. These initial meetings resulted in the development of an outline of what was considered to be the key components of a self-diagnostic tool. These components were; a clinical description of MC, good clear images of lesions, and images and/or text describing other common conditions which parents might confuse for MC to help distinguish these from MC.

The instrument and format initially chosen to be used for the parental diagnostic tool was a simple single sided sheet of A4 paper with printed images and text.

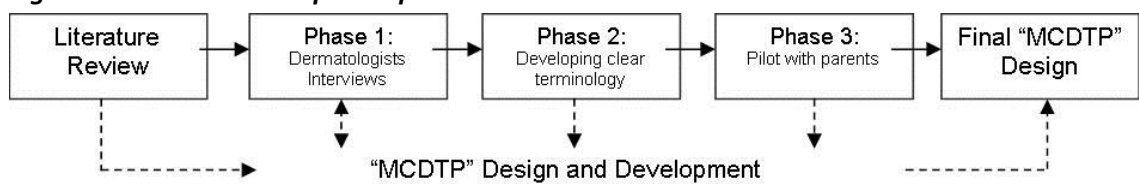
For the purposes of discussions and in line with other diagnostic tools, the final tool designed was given a title of the 'Molluscum Contagiosum Diagnostic Tool for Parents (MCDTP)'. The final name was created following discussions with the project team and involved feedback from a dermatologist specialist nurse as to whether this would be acceptable in clinical practice. For the remainder of the thesis and in all study materials the tool that was designed in this chapter is referred to as the MCDTP.

⁶ Vincent Piguet (VP), Professor of Dermatology. NF, JG and VP were academic supervisors for this thesis.

5.2.2 Development process summary

A thorough development process was formed which included the following steps: outlining a clinical diagnosis of MC with experts, ensuring clear understandable terms were used, and a pilot with parents to test its usability. These three phases of the MCDTP development are shown in Figure 15 and the procedures summarised below;

Figure 15. MCDTP development process



Phase one: Nine dermatologists participated in semi-structured interviews to establish the key components of diagnosing MC and identify images which were most typical of MC. Photographic images of MC lesions came from a selection extracted from the Cardiff and Vale University Health Board medical image library.

Phase two: The findings from the dermatologist interviews were tabulated and summarised, then discussed in interviews with a patient representative, a school nurse, and a dermatology specialist nurse. The data from these interviews were discussed in project management meetings and used to produce a first draft of the MCDTP.

Phase three: The initial design of the MCDTP was piloted at a local parent network meeting with 12 members in Cardiff, Wales. The aim of this pilot was to ensure the instructions and wording of the tool were clear, and that parents would be willing to use the MCDTP to diagnose their child's skin lesion. Following the pilot the findings were discussed at a project management meeting to assess if further changes were required to the MCDTP.

5.3 Approvals and Consent

Consent was gained prior to conducting interviews or inviting participants to complete the study questionnaires. Each participant was given verbal information about the study, handed a

participant information sheet, and given the opportunity to ask questions about their participation. Interviews were only conducted once this consent had been granted.

Each study phase received a favourable ethical opinion prior to commencement by the NHS NRES South Central-Berkshire B board (12/SC/0455). For phase one and two where the research was conducted with NHS staff and potentially on NHS premises, R&D approval was granted by Cardiff and Vale University Health Board (12/CMC/5055) (Appendix 5.2). I was issued with a letter of access to conduct the study with NHS staff and on NHS premises within Cardiff and Vale UHB jurisdiction (Appendix 5.7).

5.4 Phase one: Establishing key features of MC

5.4.1 Initial literature review of clinical diagnosis of MC

The first step of the development process was to establish the clinical diagnosis of MC through the process of a brief review of the published literature. For the brief review I, supported by VP (Professor of dermatology), conducted a search of dermatology textbooks, and recently published clinical reviews for the description of the key diagnosis features.

5.4.1.1 Results of brief review

MC is most commonly diagnosed following a clinical examination of lesion appearance by general practitioners or dermatologists, and can also be confirmed by the histopathology found in biopsies of lesions (3, 4); although biopsies are rare and they generally only occur in unusual cases. The clinical summary of MC is of single or multiple clusters of wart-like pearlescent lesions which can appear anywhere on the body (5), formed of slightly raised lesions of rubbery consistency up to 5mm in diameter (1). They are characterised by small, discreet, waxy, skin-coloured, dome-shaped papules presenting as generally less than 20 in immunocompetent hosts (7). The Rook Textbook of Clinical Dermatology (120) describe MC as spots on the skin, which are flesh-coloured, domed shaped papules with a central depression. This umbilication or central depression is the most important diagnostic sign, however may not

be present in all lesions. A description in the textbook Dermatology by Rapini R et al (121) describe MC lesions as firm, umbilicated, pearly papules with a waxy surface.

This description from the published literature formed the basis of the MC diagnosis; this was combined with current clinical practices for diagnosing MC that was established during the following interviews with dermatologists.

5.4.2 Study design for Dermatologist interviews

I conducted a series of semi-structured interviews with experts (dermatologists) to establish the key visual diagnostic characteristics of MC. Structured interviews were conducted using a structured topic guide/interview questionnaire (Appendix 3.1) and both open and closed questions were used. This approach was selected because the aim was to generate 'hard' data based on unequivocal measures (122) to describe the facts of what is the clinical diagnosis of MC, and how is this diagnosis made (123). Other approaches that were considered include non-structured interviews and focus groups. These were deemed less suitable because although both methods would have generated rich data from the discussions about personal 'experiences', 'behaviours', and 'attitudes' towards diagnosing MC, they may not have answered the specific aim. The aim was relatively simple, and for a senior clinician diagnosing a common self-limiting condition such as MC, it would not require great perspectival thinking or discussion. Both focus groups and non-structured interviews can be time consuming and costly due to training involved, the need of facilitation, and extended time of interviews for the participants taking part (123).

Where possible, interviews were conducted face to face but if where this was not possible a telephone interview was conducted. As this was a brief interview of a non-sensitive topic, telephone interviews are found to be as effective in terms of providing equal accuracy rates as when conducting them face to face (124).

5.4.2.1 Selection of images

The MCDTP relies greatly on the images of MC used and therefore those images used required careful consideration. To select these images, dermatologists were shown 10 images of MC and asked to select those that they felt were most representative of MC lesions seen in clinic, noting what attributes of the images should be emphasised to aid a diagnosis. The initial 10 images were selected by AA⁷ from the Cardiff University medical image library.

5.4.2.2 Participants

Dermatologists were recruited from University Hospital of Wales (UHW) following identification by the Head of Department of Dermatology and Academic Wound Healing (VP). Participants were eligible to take part if they were either consultant or registrar level dermatologists currently working within the department to ensure expert opinion in the design of the MCDTP. They were also selected by their availability for interview. Each participant was sent an email inviting them to participate. Of 11 invited, nine agreed to participate, one was currently on maternity leave, and one did not respond. Dermatologists were selected to act as key informants and provide specific information of the key diagnostic criteria of MC to aid the development of the self-diagnostic tool. Selecting Dermatologists as key informants allowed experts to be purposefully identified for the gathering of specific information which may not be otherwise available (125). For the purposes of this study, they were recruited to gain a particular understanding of diagnosing MC by experts in the field.

5.4.2.3 Procedure

Interviews were conducted at the preferred location of the participants. In the majority of cases (n=5) they were in the individual participant's office in Glamorgan House (UHW), or in a clinical consultation room prior to a clinical session (n=3). One interview was conducted over the telephone where materials were sent prior to the interview and the participant was asked to have these available on their computer screen during the phone interview. The interviews

⁷ Alex Anstey (AA), Professor of Dermatology.

were conducted following a structured interview plan; responses were written down during the interview by the interviewer (myself).

5.4.2.4 Analysis

A thematic analysis was used to group together the results of the interviews with Dermatologists. Although this study conducted a short structured interview with a relatively small number of participants, the thematic approach was beneficial due to the exact uses and measurements not being defined (126).

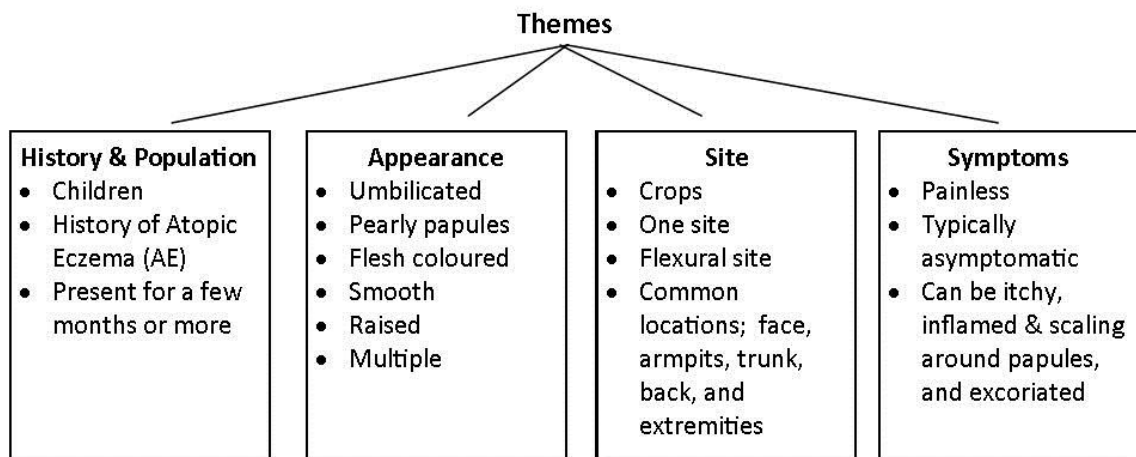
For the purposes of selecting images of MC for the MCDTP, each image marked as appropriate during the interview phase were counted. The four with the highest count were used.

5.4.3 Results: Text selected for MCDTP

The responses from the nine dermatologist interviews were tabulated by question; these were then grouped into key emerging themes which were constant throughout all of the responses to signify that they were important features for a diagnosis of MC.

The responses were grouped into the following categories; History & population, appearance, site, and symptoms. Figure 16 shows terms which were grouped into these categories following analysis.

Figure 16. Key categories and text for diagnosing MC by Themes



5.5 Phase two: Improving usability of MCDTP

5.5.1 Medical terminology

It is important to be aware when producing documents for public use that the same words can mean different things to different people or may not be understood at all (127). To avoid any potential misunderstanding by parents of the commonly used medical terms which were used by clinicians in describing MC there must be careful consideration of the final wording used in the MCDTP. The interpretation of medical terms by doctors and patients can be significantly different (128), and even the most commonly used medical terminology should be carefully explained to parents to avoid confusion (129). The differences between doctors and patients choices of definitions can be clearly different; however other health professionals can bridge the gap between the two groups (130). Ensuring that what is meant in the terms is clearly relayed, the choice of wording can ensure that there is effective communication between clinicians and patients (130), and for the purposes of designing the MCDTP, wording is an essential element to its usability.

5.5.2 Study Design

This phase conducted an informal conversation/interview aiming to gain rich detailed answers to a brief specific guide to generate the most suitable lay terminology for use in the MCDTP.

Following phase one a brief guide of medical terminology was established; this then formed a checklist/prompt which was used for the interview (Appendix 3.2). The interview style used for this phase is referred to as 'unstructured' (131) or an interview with a 'general interview guide' (132). This method is beneficial for allowing the probing or expansion of a set group of points in a conversational style; the wording of the questions is not set but is spontaneous depending on the flow of the interview. It is important that the integrity of the terms highlighted from the earlier dermatologist interviews were translated into a lay language, understandable to parents but also maintaining the same meaning and therefore this style of probing and questioning participant responses is useful.

5.5.2.1 Participants

As described previously, in bridging the gap between terms used by doctors and the meaning being understood by patients, other health professionals can be key. Therefore in this study phase practicing healthcare professionals who have regular contact with parents were selected to take part. A school nurse from the local health authority was emailed and agreed to participate, as was a dermatology speciality nurse from UHW. Recruiting both a school nurse and dermatology specialist nurse, utilised the experience of health professionals who regularly relay medical information directly to parents and their children. The dermatology specialist nurse also added value due to a specialist background in skin conditions. SW, patient representative, also participated in a separate interview using a similar format. Including patients or members of the public within planning and implementation of the MCDTP helps to ensure that it will be more reliable and relevant to the end users' needs and concerns (133). Using a patient representative in the initial design of the MCDTP helped by making the information more relevant to people affected by MC, ensuring it contains all the information parents would want to know and making the tool more accessible by eliminating jargon (134).

5.5.2.2 Procedure

I conducted two informal meetings firstly with health professionals, and secondly with a patient representative to discuss the wording of the clinical diagnosis of MC which would be used in the final MCDTP. Participants were asked to respond to questions about medical terms with suggestions of what language they would use during their day to day clinical practice.

The first meeting included the school nurse, dermatology specialist nurse and I at the Public Health Wales office, Cardiff using the structure developed from phase one. Following this meeting a first draft of the MCDTP was developed. The second meeting between SW, patient representative, and I at NM, Cardiff University used a first draft of the MCDTP as a guide to discuss the potential wording used.

5.5.3 Data Collection

Notes were made during the two informal meetings. Wording and phrases were tabulated and matched against that in the schedule. Any expansions or advice on how to describe dermatological conditions based upon the participants experience were also noted.

5.5.4 Analysis

5.5.4.1 Wording

The analysis conducted was to match the wording from the results of phase one to terms which were considered to be clear and concise for lay readers. Notes made using the interview schedule were tabulated to show matching words (Table 25). The analysis was split into two sections; original wording and recommended words to aid parental diagnosis using a paper tool.

Table 25. Recommended wording for use in MCDTP

Category	Original wording	Recommended wording
Lesion	Lesion	Spot Spot, lump or bump
Appearance	Umbilicated Flesh Coloured Smooth / Raised Multiple	Little dimple in the centre Same colour as skin Smooth / raised & show in image Multiple & show image of multiple lesions
Site	Crops / One site Locations	Multiple normally appearing in just one area Tummy, back, arms, legs or face
Symptoms	Asymptomatic / Painless Itchy Inflamed and scaling around papules, and excoriated	Usually painless Can be itchy If the spots are scratched they may look red and sore

5.5.4.2 Further recommendations

During the first interview both the school and dermatology nurses stressed that a diagnosis would not be possible without any images of common MC lesions in the final MCDTP. There was also a recommendation for the lesions images to be clearly annotated to highlight any features which would aid a diagnosis.

It was recommended that the MCDTP should exclude information of a history of AE and the duration of lesions; both of which were earlier described by dermatologists as factors which may help a diagnosis of MC. However, the nurses argued that as AE may not be present in all children with MC this may wrongly influence parent diagnosis or cause confusion, and that including the duration of lesions may also lead to confusion as the potential study participants would be visiting their doctors at various stages of the virus.

Both dermatologists and nurse participants noted that although the features described are of typical MC lesions, not all lesions within a cluster may have the same distinctive characteristics that are seen in most MC lesions. Therefore it was recommended to use wording such as 'typically', 'usually', 'normally', 'most common', and 'may look' within the descriptive text as this will imply that although these are important features, they may not be typical in each lesion.

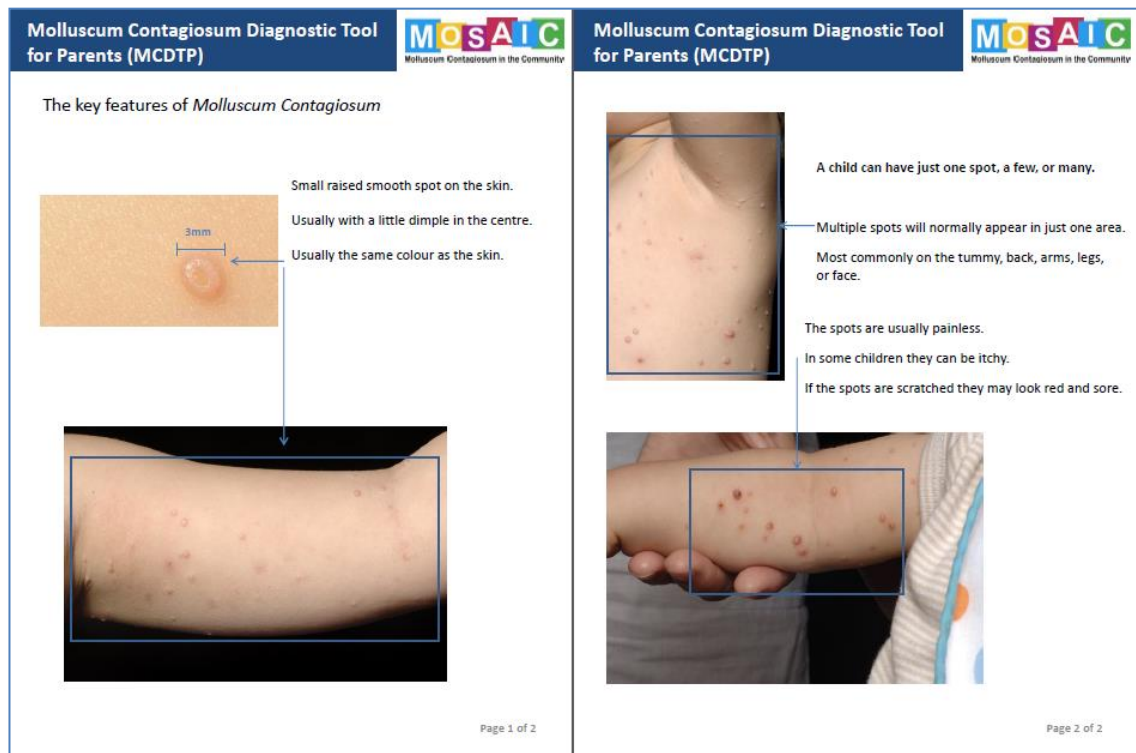
Finally it was suggested that including other conditions which MC could be misdiagnosed as should be removed from the MCDTP. It was thought this would lead to confusion with users and as the MCDTP will provide a comprehensive description of MC that distinguishes it from other conditions, then this information would not be required to aid a diagnosis.

5.5.5 Results: Draft MCDTP

The first draft of the MCDTP was made following this second stage in the development process using the images, suggested wording and annotation recommended. The initial document was shared with the project team for feedback, slight edits were made and a final first draft was produced to pilot with parents (Figure 17).

The initial design and layout of the MCDTP was completed using Microsoft PowerPoint to produce a pdf version for use in the pilot phase. The design phase aimed to produce an attractive and well laid out tool with clear instructions on how it should be completed, which is important for the design of questionnaires used in research (127).

Figure 17. First draft MCDTP



5.6 Phase three: pilot of MCDTP

5.6.1 Introduction

Phase three of the development process aimed to test the MCDTP for its comprehensiveness and usability with a small group of the population of interest (135). For the purposes of the MCDTP and its future use, the most relevant group for testing were parents with no clinical background.

5.6.2 Study Design

The study design was an observational pilot study of a group of parents attending a local parent network meeting. The pilot aimed to understand whether there were any concerns with the flow and use of the 'MCDTP', if any questions were being missed by respondents, or if the 'MCDTP' highlighted any issues in the process of diagnosing MC by parents.

5.6.2.1 Participants

Parents attending a local parent network in Cardiff were invited to take part in the research. The group was identified following an online search of local parent groups in Cardiff. The search found the 'Cardiff Parent Network', whose website outlined that this group has a specific purpose of bringing local parents together to meet other parents, discuss their views, and influence services for children and families. I initially contacted the network co-ordinator/chair via email, outlining the study and asking for permission to attend a future meeting to conduct a small pilot of the MCDTP. It is important to note this group had no specific interest in research or a purpose to review research projects.

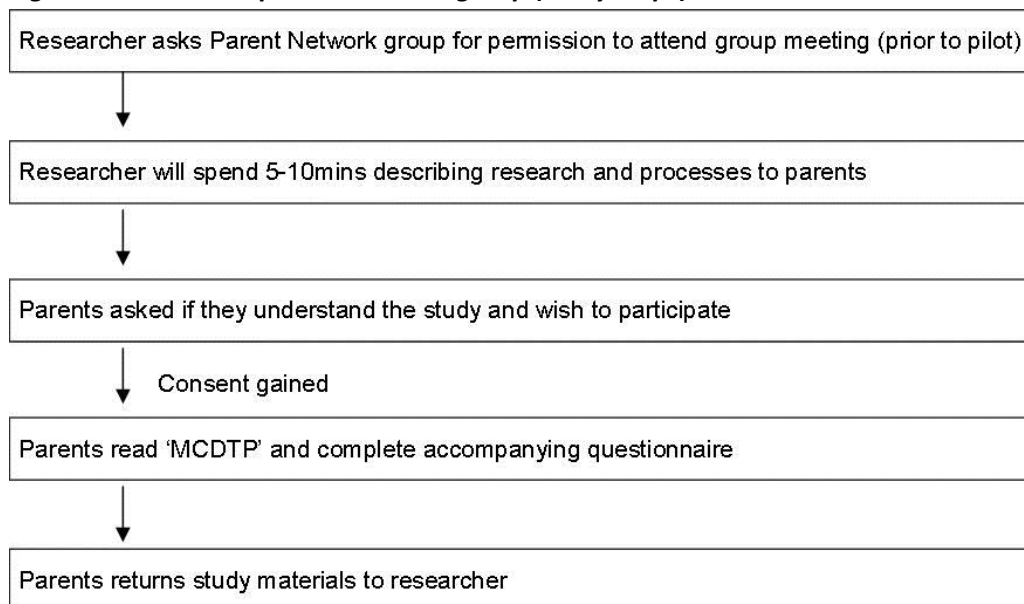
5.6.2.2 Procedure

The study procedure followed a structure outlined in Figure 18. Data was collected using a semi-structured questionnaire consisting of two questions and a 'free text' area. This method was chosen as the preferred data collection method due to its ability to ask directly about the

points concerned with the research, and its benefits of being a relatively cheap and easy data collection method (136).

The procedure for the pilot was as follows; the outline of the study was explained to the parents attending the group, and what their participation entailed. Once the parents consented they were given the study materials to discuss and complete. The study materials consisted of a participant information sheet, first draft version of the MCDTP, and a short semi-structured questionnaire.

Figure 18. Pilot with parent network group (study steps)



5.6.3 Data Collection and Analysis

Data was collected on paper questionnaire forms (Appendix 3.3). The data was entered into Microsoft Excel for descriptive analysis. Parents were asked to note all of their comments on the data collection forms but if there was any further verbal feedback, I included this in my own notes and within the results.

5.6.4 Results

The group meeting took place in a local community and children centre in Riverside, Cardiff in December 2012. A total of 12 parents attended the session as well as the chair (an employee

of Cardiff City Council) and a local government commissioning manager who was observing the session.

Generally the feedback to understanding the questionnaire and if parents would be willing to complete the MCDTP if they were asked to in a GP surgery was positive, where 11 of the 12 respondents indicated yes to both questions (Table 26).

Table 26. Feedback questionnaire to MCDTP

	Yes	No
Q1) Did you understand the instructions?	11 (92%)	1 (8%)
Q2) Would you be happy to complete the questionnaire on behalf of your child?	11 (92%)	1 (8%)

Participants were also asked to provide additional feedback after reading the MCDTP; eight of the 12 participants provided additional feedback. Generally feedback was positive (n=5/8), three gave short positive descriptions;

“was useful to know.” [P01]

“fine.” [P02]

“Can be handy, will take the scare out of the symptoms.” [P03]

Two participants suggested parents would like to have more information about MC, and one indicated that information about common conditions in children should be sent to all parents when their child begins school;

“A leaflet sent to school would be useful to raise awareness.” [P06]

“Instructions were clear. Clear instructions and pictures, easy to follow. No info on MC.

More info on how long it lasts would be good if poss.” [P09]

Some parents were confused with the purpose of the tool, not knowing why this would be used in GP surgeries when parents were already attending the practice to see a doctor, and that the exact use was unclear;

“Confusing as to the use, why self-diagnose if having to go to the GP?” [P07]

“Confusing at first.” [P08]

“some of the info is contradictory and confusing.” [P11]

As the instructions and compliance to complete the MCDTP in GP surgeries was positive (11 of 12 indicating they would), there were no further changes required to the draft MCDTP. The additional ‘free text’ feedback suggests that the MCDTP instructions may not be clear.

5.6.5 Conclusions of pilot phase

The two page MCDTP was found to be acceptable to parents where 92% (n=11/12) of parents indicated they understood the MCDTP and would completed it if asked in a GP surgery; suggesting that this version of the MCDTP can be used in the subsequent validation phase. However, a key finding from the pilot and an area which did confuse some parents was the exact purpose of the MCDTP and why they would be asked to look at the document in a GP surgery. This feedback suggests that before assessing the extent to which the instrument is valid the instructions featured on the MCDTP, in describing why parents are being asked to complete it in the GP surgery, need to be clearer and more concise to avoid confusion.

During the session the parents were instantly engaged in the study, they were very curious about knowing exactly what the research was and the overall study aims. As I attended the session I explained the overall aims of the wider MOSAIC study and this became a discussion point. This may have caused confusion with parents as to how a self-diagnostic tool would fit into these wider aims and the confusion may have been caused by myself. On reflection, and if I were to replicated this pilot phase again, I would not explain the overall study to the

participants but keep my explanation only to the aims of the study phase which were being conducted on that day. The group who took part in the pilot was well established and had been meeting monthly for over 12 months, all members were confident to voice any questions they had about the research. These questions did snowball where the more questions that I provided answers to, the more questions about the whole research project and about MC in general were raised. To ensure the objective of the pilot was achieved within the timescale allocated to myself during the meeting, I made a conscious effort to gently stop any further questions that weren't about the MCDTP and to ask the group to complete the questionnaires and ensure that they noted all of the points they had raised in voice within the paper form.

5.6.6 Outcome: Final MCDTP

Feedback from the pilot did not highlight that there were any changes needed to the design of the MCDTP as the majority of parents indicated that the language was understandable and they would be willing to complete the MCDTP on behalf of their child if asked in a GP surgery. Feedback indicated that the overall instructions were not clear as to why they were completing the MCDTP and what it would be used for. This is an area of the design that must be made clearer when assessing the validity of the MCDTP as a parental diagnostic instrument to ensure participants understand what they are required to do and why.

5.7 Discussion

The MCDTP was developed using a framework established by epidemiologists (112) to produce a good disease definition for the purpose of epidemiological studies. How these elements have been incorporated into the final MCDTP are shown in Table 27.

The first draft of the MCDTP did change from the initial designs that were discussed in the early meetings of the project management group. The changes made were following feedback given during the development stages and these were; the section describing the key diagnosis differences from other conditions were excluded, and images of MC lesions were annotated

with the key diagnostic features. Important elements incorporated into the MCDTP were that it was clear, ensuring simple wording was used with no medical jargon, and that it maintained the key diagnostic elements provided by experts.

Table 27. MCDTP disease definition framework

Disease definition characteristic	Incorporation in MCDTP
Valid (sensitivity and specificity)	Measured in subsequent chapter (chapter six).
Repeatable	The developed MCDTP is a tool which will can be reproduced and used for all participants who were asked to take part in this study (chapter seven) or potentially in other epidemiological studies.
Acceptable to population	This is a non-invasive test. Feedback from pilot shows the procedure of completing the MCDTP is acceptable to parents and that parents would complete the MCDTP if asked when attending a GP surgery.
Rapid and easy to perform	The MCDTP has been designed with the intention of being short and concise with and ability to be completed while parents wait to see the doctor in the GP surgery waiting area. Areas which may have confused have been excluded following the pilot phase. For clinicians, they will diagnose the lesion and note a yes/no diagnosis question – keeping the impact upon consultation to a minimum. The exact features of how the test will be performed are described in chapter six of this thesis.
Coherent with prevailing clinical concepts	A brief review of current clinical textbook and publications along with practicing dermatologists (n=9) were included in the development of the MC diagnosis to ensure key elements for the current disease syndrome were included.
Reflect some degree of disease morbidity	The MCDTP highlights the features of common MC seen in primary care; therefore it must be acknowledged that it may not be suitable for unusual and rare cases.
Comprehensive in its application	The principle use of the MCDTP is in the UK which has a predominately White English speaking population. The features of MC are mirrored in ethnic skin types however the images used in the MCDTP do not features any other skin types than white.

Disease definition characteristic	Incorporation in MCDTP
Inclusion of elements comparable with other studies	The majority of studies of children with MC confirm a diagnosis of MC given by a medical practitioner, or in some cases self-reported of a previous diagnosis. This is the first parental diagnosis tool to for MC in children that will be tested in primary care.

5.7.1 Potential limitations in the development of the MCDTP

5.7.1.1 Potential limitations of using the MCDTP to identify MC

A limitation of the MCDTP is that it may not be suitable for identifying unusual and rare cases of MC, as in these cases where a diagnosis is difficult or uncertain they are sometimes referred for biopsy to confirm a diagnosis. The skin colour of all the images used in the final MCDTP is of children with white skin, therefore its acceptability to other more diverse populations needs to be considered. The external validity of the MCDTP and its acceptability to the populations of Cardiff, Wales, and England will be discussed further in chapter six of the thesis.

5.7.1.2 Potential limitations in the data collection methods

During the interviews with key stakeholders and other phases of the MCDTP development field notes were taken to collect study data and these notes were later used for data analysis. Collecting data in this way is inevitably selective and subjective to observer bias (137). Although this method was an efficient way of collecting data that was cheap, non-intrusive and freely available independently of budget and time available, alternative methods were available for data collection. These alternative methods were tape or video recording, however these methods can be expensive in equipment costs, transcription and coding, and they also can be deemed intrusive by study participants.

The interviews conducted in this study phase had a narrow and pre-defined scope, and this provided direct interviews generating responses that required little philosophical

interpretation therefore reducing potential errors in reporting of results through the method of data collection. Collecting study data and observing interviews myself was also an important of the research process as it allowed me to “see for myself” how responses were given and aided in the interpretation of findings. In terms of personal development it also allowed me to gain interview skills and confidence in the processes of research.

5.7.1.3 Potential limitations of participants

Dermatologists were selected to provide an ‘expert’ diagnosis of MC from their clinical training, experience and knowledge, however it can be argued that it is GPs who see the most cases of MC in the UK and therefore they could have been selected as ‘experts’ to provide this knowledge. Although GPs could have feasibly participated in the research to provide this diagnosis of MC, dermatologists were chosen due to their position as being the experts in diagnosing skin conditions in the UK, however using either medical specialty would have brought its own limitations.

The parent group used for the pilot of the MCDTP may not be representative of the target population who will completed it in GP surgeries. The group consisted of local parents (n=12) that were formed as a local community group by Cardiff Council in a largely socially deprived area of the city, rather than a mix of parents from differing demographic backgrounds brought together for research purposes. No data was collected of the parents such as age, educational level, postcode (to derive socio-economic status) that would provide further description of the group or to compare if there were any differences in these characteristics between parents who provided positive or negative feedback. Although focus groups are found to be useful for testing the paraphrasing of questions, the MCDTP was tested with only this group rather than in multiple group sessions which are recommended in qualitative research (138). However, due to the training, time and cost constraints associated with conducting focus groups the

benefits of using a well-established freely available group to receive feedback of the MCDTP usability was beneficial to this research phase.

5.8 Conclusions

The overall feedback from the pilot study shows that the MCDTP is understandable and parents were positive that they would complete it if asked in a GP surgery. However some participants provided feedback that the general instructions of why they were completing the MCDTP were confusing, highlighting further development was required before assessing the validity of the instrument to ensure that the wording of the instructions are clear and concise when handed to parents.

The subsequent chapter will assess the extent to which the MCDTP is valid by describing its effectiveness in supporting parents to diagnose MC when their diagnosis is compared to a GP.

Chapter six: Assessing the extent to which the MCDTP is valid as a parental molluscum contagiosum diagnostic tool

The development and validation of the MCDTP was published as an original research article in the *British Journal of General Practice*. A copy of the published paper can be found in Appendix 1.2.

6. Overview

This chapter will describe the extent to which the MCDTP that was developed in the previous chapter is valid as a parental diagnostic tool for MC. The diagnosis of a parent (index test) was compared to that of a GP (gold standard) to measure the accuracy of the MCDTP as a diagnostic tool for MC. This chapter will define the study design, setting, procedure, and results of this assessment. The chapter will conclude by discussing the potential limitations of this study.

6.1 Objectives

6.1.1 Primary Objective

The primary object of this study phase was to measure the accuracy of parental diagnosis of their child's skin lesion as MC or not, when supported by use of the MCDTP, compared to a gold standard of GP diagnosis of the skin lesion.

6.1.2 Secondary objectives

The secondary objectives were to;

- Explore the relationship between parental confidence in their diagnosis and agreement with the gold standard.
- Describe the inter-rater agreement between the gold standard test (GP diagnosis) and diagnosis made by a panel of expert clinicians.

6.2 Study design

Following development of the MCDTP (which involved three phases with dermatologists, nurses, GPs and parents, described in chapter five) the diagnostic accuracy was assessed. The diagnostic accuracy was measured using data from two tests; an index test performed by the child's parent, and reference standard (gold standard) performed by a clinician. Inter-rater agreement was measured between the reference standard test (GP diagnosis) and diagnosis made by a panel of expert clinicians where photographs of a sample of participants were obtained, allowing a diagnosis of MC to be made independently by three further clinicians.

6.2.1 Index test

Parents of children, aged one to 14 years, completed the index test. The index test consisted of parents of children with a skin lesion viewing and reading the images and text within the MCDTP. They would then use this to make an educated decision on whether their child's skin lesions were MC or not. The test was performed prior to a child's consultation with their GP. Parents were asked to mark how confident they were in making that decision on a scale of 'Very Confident', 'Confident', 'A bit confident' or 'Not confident'.

6.2.2 Reference test

The reference test was completed by the child's GP. This was conducted during the subsequent consultation where a clinical examination of the child's skin lesion was performed and the GP noted a yes/no diagnosis of MC.

6.2.2.1 Rational for reference test

GP clinical diagnosis was selected as the reference test. The gold standard diagnosis for MC would be performed following biopsy (4); however parents may be uncomfortable with this test being performed on their child for research purposes. Adding intrusive or burdensome methods to the study may reduce participation rates not only by parents (139), but also the research sites. Conducting a more comprehensive procedure would require practitioner

training and impact on clinical time which may not have been appealing to all sites. GP diagnosis was deemed the most rational selection for our reference test as (within the UK) most cases of MC will be seen in primary care and diagnosed by a GP. Only the most rare and unusual cases will be referred to a dermatologist. GP's will be accustomed to diagnosing MC as part of their usual practice. Furthermore, a two-page information sheet about MC was provided to each GP who participated in the study (appendix 3.4) as a guide to the most common features of the condition.

Dermatologists could have been used as the reference standard test, and a similar study design as outlined for GP surgeries could have been used in a dermatology outpatient clinic setting. Dermatologists specialise in diagnosing skin conditions, and may be viewed by some as the next best gold standard to a biopsy for a confirmed MC diagnosis. There is no evidence supporting whether a GP or dermatologist provide better diagnostic accuracy for MC when compared to a biopsy. However MC is typically rarely seen in dermatology clinics and within the UK patients with MC will normally present and be diagnosed in primary care. Indeed, children attending dermatology clinics would have provided a higher proportion of children with a skin lesion, and this subsequently may have shortened the recruitment timetable, or provided an increased sample size. However in dermatology clinics there may have been a much lower proportion of skin lesions being MC due to the condition being seen in this setting infrequently. Parents of children visiting a dermatologist may be accustomed to examining their child's skin and in addition may have already received diagnostic information from the GP during the original consultation, impacting on their own diagnosis of MC. Performing the test in a dermatology clinic scenario may have introduced selection bias meaning the results were not generalisable to the wider population. Inviting parents and their children, who completed the index test in GP surgeries, to have the reference test conducted whilst attending their local GP practices provides a readily available population which is representative of the wider population in the UK.

6.2.3 Inclusion and exclusion criteria

The inclusion criteria were children aged one to 14 years attending a consultation with a primary care general practitioner (GP) and having a skin lesion.

Children were excluded if they currently or had previously been diagnosed with MC by their GP.

6.2.4 Setting

The setting for completion of the MCDTP was in primary care surgeries within the geographic area of Cardiff and the Vale of Glamorgan, and governance of Cardiff and Vale University Health Board (UHB). This setting was selected as it ensured that both the index and reference test could be carried out on the same day with minimum impact upon both the parent and GP. Conducting the research within Cardiff and the Vale of Glamorgan meant all sites were within a daily commutable distance from Cardiff University, and allowed the researcher (myself) to be able to travel to research sites for recruitment. Only parents with children attending the surgery for a GP consultation on that day were asked to participate.

6.2.5 Research sites

All GP practices within Cardiff and Vale UHB (n=92) were invited to participate in the research study. Each practice manager received a letter (appendix 3.5) that explained the study procedure, what the study would involve for the practice and invited them to participate. Practices who participate in teledermatology at UHW were also emailed the same letter directly to the teledermatology administrator at the practice from the Head of Department of Dermatology, UHW. As the study was a NISCHR CRC registered project, recruitment of sites was supported through the South East Wales Network Team who raised awareness of the study through their established practice network.

In total 16 practices responded to the materials which were sent, indicating they had reviewed the study during a senior partner practice management meeting. Of those 16 who responded, 12 indicated that they would like to participate in the study and four declined. Five of the 12 practices agreed to participate in the additional phase of obtaining photographs of skin lesions.

6.2.6 Screening

To narrow the selection of ineligible children participating in the study, parents were screened before receiving information about the study. Firstly, the child was screened by age, as only children aged one to 14 years were eligible to participate in the study. Secondly, only children with skin lesions were required for the study. Although the term 'lesion' is commonly used and acceptable by medical practitioners, this may not be the case in the general population and could lead to misinterpretation and/or confusion. During the development of the MCDTP recommended wording for 'lesion' in patient facing documents was defined as 'a spot, lump or bump'.

Children were screened upon entering a practice if they were within the age range, and answered yes to the screening question of 'having a spot, lump or bump on the skin'. The screening wordings were printed on a study pack envelope (Appendix 3.6) which was handed to parents by reception staff.

6.2.7 Providing clear instructions to parents completing the MCDTP

Within the development phase of the MCDTP a key conclusion was that the instructions for using the tool and why parents were being asked to participate were not clear, and this caused confusion for some parents who participated in the pilot. To improve the instructions and usability of the MCDTP a front and back page were added to the MCDTP to form an A5 booklet. The front page provided clear instructions of the study steps for participating parents using cartoons and text. On the back page parents and GP's were guided as to which sections they should complete and what to do next. During discussions with SW, a lay representative,

she suggested that simple and clear instructions about the study should also be included on the study envelope. A draft study envelope was produced and discussed with SW who provided feedback on all content within the study envelopment that was used.

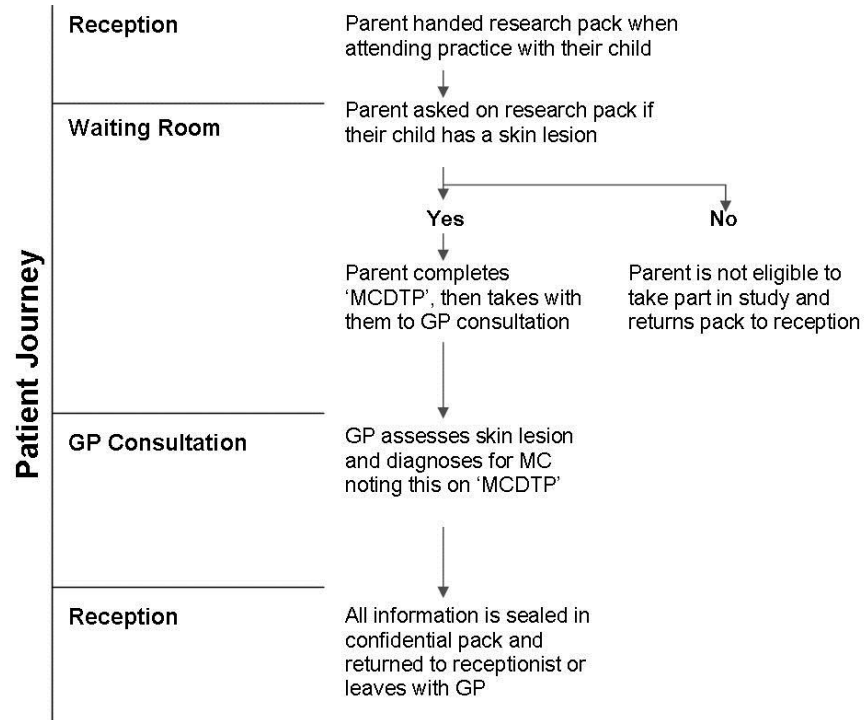
6.2.8 The 'study pack'

The study pack which was given to each participant by the receptionist at the practice contained the following; participant information sheet, information sheet for children, consent form, assent form, 'MCDTP', and a pen. These documents were inserted into an A5 white envelope with the screening questions and brief information about the study printed on the front (Appendix 3.6).

6.2.9 Procedure

Parents of children, aged one to 14 with skin lesion/s, were asked to read the study materials, provide consent, and complete the MCDTP in the practice waiting area prior to their consultation with a GP (index test) noting on the form whether they would diagnose their child's skin lesion as MC. Parents also marked how confident they were in making that decision on a scale of 'Very Confident', 'Confident', 'A bit confident' or 'Not confident'. During their consultation a clinical examination of the lesion was performed by the GP (reference standard), who noted a yes/no diagnosis of MC. The index and reference tests were performed on the same day. The complete procedure in GP surgeries following the patient journey is shown in Figure 19.

Figure 19. MCDTP study process in GP practices



6.3 Inter-rater agreement

6.3.1 Design and outcome

Photographs of 20 participants' skin lesions (10% of total sample) were obtained. Two consultant dermatologists and a second GP independently reviewed these photographs to measure agreement between the MC diagnoses given by the reference standard (GP). The photographs were taken of the singular lesion, or group of lesions which the parents viewed when making a diagnosis using the MCDTP.

The three photographs assessors, GP and two dermatologists, viewed each of the images independently making an MC diagnosis solely using the photographs using the following options; negative, suspect negative, positive, suspect positive

6.3.2 Procedure

Although many GPs do indeed take photographs of skin conditions for purposes such as teledermatology, not all practices participating in this study were part of this. Therefore not all

sites would have had prior training in medical photography and access to cameras or equipment. To reduce equipment costs, photographs were taken using a camera (Camera model: Olympus SP-620UZ) loaned by the South Wales Trials Unit (SEWTU) for research purposes, and each photograph was taken by myself.

Photographs were taken whilst I attended GP practices for recruitment, all parents who participated in the study during July to September 2013, across five practice sites, were asked if they would like to take part in the additional stage of providing images. Five sites participated in this additional stage. The photographs were taken in a designated consultation room within the practice whilst the parents and their child waited to see the GP once they had completed the MCDTP.

Parents who participated in this study phase completed additional consent for the photographs to be taken.

6.3.3 Training

I undertook a one hour training session with a medical photographer from the Media Resources Centre, UHW. During this training session I was guided through the correct settings for the camera, the optimum positioning for taking the photographs, and developed a study photograph protocol to be used when in practices (appendix 3.7).

6.3.4 Outcomes

Photographs were categorised independently by each rater as MC positive, suspect MC positive, suspect MC negative or MC negative.

6.4 Recruitment

Participants were recruited at GP practice sites to complete the index test. The reference standard was completed by the GP at the research site.

The management of the study at each site was conducted by the Practice/Assistant practice manager or research manager. Their main duties were to ensure reception and clinical staff were aware of the study and trained in the study procedures. They also managed the administration of the study at the site.

6.5 Sample size

The sample size calculation was based upon achieving 90.0% sensitivity and specificity with confidence intervals of 74.4% to 96.5% (sensitivity) and 85.8% to 93.0% (specificity), and assuming an incidence of MC of 10% amongst children with a skin lesion (warts) (36, 140). This resulted in a required sample of 300 participants. As the sample size was based upon assumptions of the desired effect size and variance within the data, I planned to recalculate the sample size during the study to ensure that enough patients were recruited to give adequate power and that time was not wasted in collecting more data than necessary (141).

6.5.1 Sample size review (mid-study)

The sample size was revised by the project group following initial analysis of the first 75 participant data. The incidence of MC within this sample was 30%; higher than the 10% assumed in the original sample size calculation. The initial data was analysed and used to model the precision in the sensitivity and specificity, given a sample size of $n=200$, $n=300$ or $n=400$ and found little variation in the width of the confidence intervals. Subsequently the sample size was reduced to $n=200$ participants completing the MCDTP.

6.6 Data collection

Data was collected on the back page of the MCDTP, where the parent completed their diagnosis of MC, and how confident they were in the diagnosis. The GP then completed a small section on the same page, giving their name and ticking either 'yes' or 'no' for a diagnosis of MC. This, along with the completed consent and, where applicable, assent form were returned to the research team by the site administrator. Once returned, the data was entered into an

excel spreadsheet, the paper forms then stored within a locked cabinet in a secured office in Neuadd Meirionnydd (NM), Cardiff University.

6.7 Practice Retention

Maintaining recruitment and awareness of the study within practices was an important part of the study and as recruitment was over a period of nine months, it was essential to encourage and maintain active recruitment across all practices.

Three methods were used to maintain engagement with practices throughout the active recruitment period. Firstly, monthly newsletters were emailed to each practice; the newsletter contained recruitment updates, news about the study and tips to aid increasing recruitment in practices. Secondly, regular contact was maintained with the practices via a monthly email to the site administrator at each practice requesting the number of participants recruited, discuss how recruitment was progressing, and to arrange collection/delivery of the data forms. Finally, engagement with practices was also maintained through attendance at sites for recruitment. Although primarily the aim of attending GP surgeries was to aid and improve recruitment it also served as an opportunity to improve the relationship between the researcher (myself) and site. During attendance at GP surgeries it allowed me to speak directly to the reception staff where I could explain the study, the study procedures and also the importance of giving out the study envelopes to all parents entering the practice. Overall this was a success as many receptionists would be pleased to inform me directly that they had recruited participants during visits, however in some instances, especially larger practices with a large reception team, this did not encourage all of the reception staff to engage with the study.

6.8 Data management

Completed MCDTP forms were returned to Cardiff University where they data were entered into an excel spreadsheet. Each participant was then assigned a unique ID, practice ID, and GP ID to store the data anonymously, this additional coding was also recorded on the primary

source (MCDTP). The spreadsheet was held on a password protected computer on the Cardiff University network. Paper forms were marked as entered onto the database and then stored within a locked cabinet, on the 5th floor NM.

As a UK Clinical Research Network (UKCRN) registered study, monthly data uploads were entered onto the UKCRN portfolio database. Once uploads were completed the MOSAIC study profile was updated on the UKCRN website.

Once all data was collected, the excel file was exported into '.dta' format for analysis.

6.9 Analysis

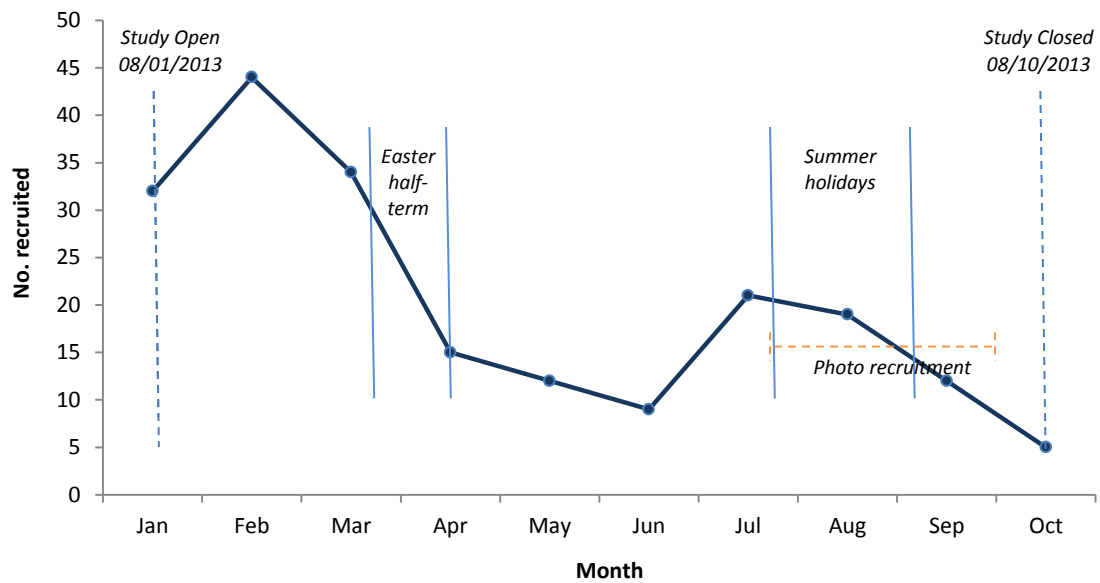
Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the MCDTP diagnosis against the reference test diagnosis were calculated. Inter-rater agreement between GP and consultant dermatologist diagnosis was also calculated. Statistical analysis was performed using STATA 12.

6.10 Results

6.10.1 Recruitment

A total of 203 parents of children aged one to 14 years participated between January and October 2013 (Figure 20). The majority of study participants were recruited within the first three months of the study opening, recruitment by month then gradually decreased to less than half of that in the initial three months. This may be due to an overall drop in awareness in each of the practices from the initial set-up and also that typically the number of consultations for children is greater in the winter months than other times in the year. Another factor may be the Easter school holiday break and build up to the summer holidays, where parents may be less likely to want to complete study documentation in a busy/hot reception area.

Figure 20. Participant recruitment in GP practices by month



60 GP's in 12 practices took part in the study. The number of participants recruited per site ranged from zero to 50 (Table 28). The sites where I personally attended to recruit participants (002, 006, 008, 010, and 012) were those with the highest numbers recruited. These sites were chosen due to having particularly poor recruitment numbers in month one; in particular site 002 was a concern as it had recruited zero participants in the first month, and had not previously participated in a research study. However, once I attended the practice and spoke directly with the reception/clinical staff where I could explain the study, this site ended the study period being the highest recruiters. Other factors may well have influenced the high recruitment such as being centrally located in a large family housing estate. However due to the initial poor start I conclude that the impact of engaging directly with the practice positively impacted on the overall recruitment. Other sites I chose to attend were selected partially due to good accessibility via public transport and a willingness to allow a researcher to attend the site for recruitment. Although site 012 had low recruitment, the site joined the study in the final month (August 2013) when a new practice manager was appointed with experience in research.

Participants were evenly distributed between genders, and the majority aged one to three years (40%) (Table 29).

Table 28. Participants recruited by practice site

Practice Code	Location	IMD score*	Rural/Urban classification**	No. Recruited	No. GP's completing MCDTP
001	Cardiff	46.72	Urban >10k	18	9
002	Cardiff	1.22	Urban >10k	50	5
003	Cardiff	8.54	Urban >10k	4	2
004	Cardiff	10.53	Urban >10k	12	4
005	Vale of Glamorgan	8.58	Urban >10k	7	5
006	Vale of Glamorgan	10.44	Urban >10k	28	7
007	Vale of Glamorgan	10.44	Urban >10k	21	3
008	Vale of Glamorgan	8.36	Urban >10k	30	9
009	Vale of Glamorgan	26.05	Urban >10k	13	6
010	Vale of Glamorgan	23.05	Urban >10k	17	8
011	Cardiff	21.70	Urban >10k	0	n/a
012	Vale of Glamorgan	3.74	Urban >10k	3	2
<i>Total</i>				<i>203</i>	<i>60</i>

*2000 IMD scores for electoral ward (The higher the score, the higher the average level of deprivation) **2004 Rural and Urban classification for wards (Source: ONS 2007 (142))

Table 29. Participant characteristics

Age (years)	Sex (%)		Total
	Male	Female	
1 to 3	36 (44%)	45 (56%)	81 (40%)
4 to 6	25 (46%)	29 (54%)	54 (27%)
7 to 9	19 (53%)	17 (47%)	36 (18%)
10 to 14	16 (50%)	16 (50%)	32 (15%)
<i>Total</i>	<i>96 (47%)</i>	<i>107 (53%)</i>	<i>203</i>

6.10.2 Main outcome

Data on confidence in their diagnosis was provided by 186 (91.6%) parents (Table 30). Of these, 85% indicated they were either 'very confident' or 'confident' in their diagnosis.

Table 30. Agreement of MC diagnosis between GP and parent listed by parental diagnostic confidence

	Diagnosis agreement		Total
	Agree	Disagree	
Very Confident	94 (95%)	5 (5%)	99
Confident	52 (88%)	7 (12%)	59
A bit confident	17 (71%)	7 (29%)	24
Not confident	1 (25%)	3 (75%)	4
<i>Total</i>	<i>164</i>	<i>22</i>	<i>186</i>
Pearson chi2(3) = 26.5 Pr = <0.005			
Note: 17 participants did not complete this question			

Table 31 shows the incidence, sensitivity, specificity, PPV and NPV of the MCDTP by all completed, and also by only those where a parent was ‘very confident’ or ‘confident’ in their diagnosis.

The incidence of MC in the sample was 29.1% (Table 31). The sensitivity of the MCDTP was 91.5% indicating a high proportion of true positives were correctly identified by parents. The specificity was also high (88.2%) indicating that parents using the MCDTP correctly identified negative MC diagnoses. The MCDTP had a high NPV (96.2%) suggesting that the majority of parents that gave a negative diagnosis using this tool for MC were correct. However the PPV was only 76.1%, indicating that a quarter of parents who thought their child’s skin lesion was MC using this tool, may have made an incorrect diagnosis.

For parents with greater confidence in their diagnosis the incidence of MC was 30.4% with the sensitivity and specificity being 95.8% and 90.9% respectively, with a PPV of 82.1% and a NPV of 98.0%. Greater parental confidence in their diagnosis was positively associated with agreement between parental and GP diagnoses ($\chi^2 = 26.6$, $df=3$, $p<0.005$).

Table 31. Incidence of MC, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for MCDTP

a) All participants regardless of confidence in diagnosis (n=202)			
	%	95% CI	
		LCI	UCI
Incidence of MC	29.1	22.9	35.8
Sensitivity	91.5	81.3	97.2
Specificity	88.2	81.8	93.0
Positive Predictive Value (PPV)	76.1	64.5	85.4
Negative Predictive Value (NPV)	96.2	91.4	98.8
b) Participants who indicated they were 'Very Confident' or 'Confident' in their diagnosis (n=158)			
	%	95% CI	
		LCI	UCI
Incidence of MC	30.4	23.3	38.2
Sensitivity	95.8	85.7	99.5
Specificity	90.9	83.9	95.6
Positive Predictive Value (PPV)	81.2	69.9	91.1
Negative Predictive Value (NPV)	98.0	93.1	99.8

6.10.3 Inter-rater agreement

Photographs of lesions were obtained for a sample of 20 children participating in the study; 19 were used in the final analysis as one image was discarded due to poor quality (image out of focus). This was a sample of convenience where parents and their children were asked to participate in this additional study phase when attending the practice on the same date as myself.

When combined with the original assessor, overall agreement between the four clinicians was 47.4%, with a fair strength of agreement (Table 32). Comparing the initial GPs rating with the other clinicians shows varying agreement between 57.9% with Dermatologist 2, and 84.2% when compared to with GP2. The strength of the agreement is mainly fair, and there is a moderate strength between the two GP's. Each of the kappa statistics calculated between the agreements have particularly wide confidence intervals, and the overall agreement between the GP who saw the child and those who only saw the images is fair (kappa 0.31).

Table 32. Inter-rater agreement between reference standard, GP and 2 dermatologists

Diagnosis of photographs (n=19)	Agreement (%)	Kappa statistic	95% CI		Strength of agreement (143)
			LCI	UCI	
A) Agreement between GP and diagnosis made by clinician using image					
GP expert	84.2	0.52	0	1	Moderate
Dermatologist 1	68.4	0.25	0	0.97	Fair
Dermatologist 2	57.9	0.24	0	0.79	Fair
B) Agreement between clinicians viewing images					
	42.1	0.32	0.15	0.5	Fair
C) Agreement between all clinicians (reference test and those viewing image)					
	47.4	0.31	0.10	0.4	Fair

In 35% of cases, the clinicians were unable make a definitive positive or negative diagnosis for MC using the images alone, and chose to give either a suspect positive or negative diagnosis. This may be due, in some images, to the image quality; for several images the photographs were out of focus or blurred.

Table 33 provides agreement data where a 'suspected' and 'certain' diagnosis by the three photo assessors were combined. The overall agreement in diagnosis improved and was found to be high at 84.2%, with a substantial strength in agreement. In particular, the agreement between the GP expert's diagnosis and the reference standard GP was very high (94.7%), again with a substantial strength in the agreement. The agreement ranged from 84.2% to 89.5% where the reference standard was compared to the two dermatologists. Including only those assessing the images provides a high agreement, with narrow confidence intervals. This suggests that there was a very strong agreement between the three clinicians irrespective of speciality when viewing the images alone.

Table 33. Inter-rater agreement between reference standard, GP and 2 dermatologists where suspect and confirmed diagnosis is merged

Diagnosis of photographs (n=19)	Agreement (%)	Kappa statistic	95% CI		Strength of agreement (143)
			LCI	UCI	
A) Agreement between GP and diagnosis made by clinician using image					
GP expert	94.7	0.78	0.35	1	Substantial
Dermatologist 1	89.5	0.61	0.14	1	Substantial
Dermatologist 2	84.2	0.5	0.04	0.95	Moderate
B) Agreement between clinicians viewing images					
	89.5	0.79	0.74	0.84	Substantial
C) Agreement between all clinicians (reference test and those viewing image)					
	84.2	0.71	0.56	0.7	Substantial

6.11 Discussion

A total of 203 parents completed the MCDTP. The MCDTP had a sensitivity of 91.5% (95% CI 81.3 to 97.2) and a specificity of 88.2% (95% CI 81.8 to 93.0) compared to the reference standard of GP clinical diagnosis. The PPV was 76.1% (95% CI 64.5 to 85.4) and NPV 96.2% (95% CI 91.4 to 98.8) for all parents. The MCDTP was developed to act as a recruitment tool for our epidemiological study and data suggests the MCDTP is suitable for this purpose.

There was a positive association between being 'confident' in a diagnosis, and agreement in diagnosis with a clinician. This provided a sensitivity and specificity of 95.8% (95% CI 85.7 to 99.5) and 90.9% (95% CI 83.9 to 95.6) respectively in parents who were confident or very confident in their diagnosis. Excluding participants where they were 'a bit confident' or 'not confident' provided improved sensitivity, specificity, PPV and NPV.

Describing the inter-rater agreement between the reference standard test (GP diagnosis) and diagnosis made by a panel of expert clinicians was relatively fair (47.4%). This may be attributed to numerous factors such as image quality, limited patient history, and using images rather than a full consultation. Overall, 35% of the images photo assessors were unable to provide a definitive diagnosis towards either MC positive or negative, therefore giving a 'suspect' diagnosis towards positive or negative. Where the suspect diagnosis is merged, a

much higher agreement is reached (84.2%). It can be assumed that during a physical examination a diagnosis confirming a 'positive' or 'negative' MC diagnosis would have been reached. Based on this data analysis the agreement of diagnosis between 'experts' and the gold standard was substantial.

6.11.1 Comparison with other literature

Overall the agreement between clinician's diagnosis and the reference standard was substantial to moderate. Previous studies show agreement between a primary care physician's diagnosis of MC and a dermatologist as correct in up to 100% of cases (144, 145), however these were in small studies (n=8, 3) where each rater saw the patient face-to-face.

The results show that although photographs alone can be effective in providing a diagnosis, in 35% of cases this was not sufficient to make a definitive diagnosis. Although this may have been due to the quality of the image (as described above several images were blurred or out of focus), we do not know how much of the observed disagreement is related to the photographs, as there may well be disagreement even when both clinicians exam the child. This is similar to other studies of much larger numbers where 20% of dermatologists did not provide a single diagnosis using only photographs, although dermatologists were able to provide a definitive diagnosis in significantly more cases during face-to-face consultations (146). I found high levels of diagnostic agreement which are comparable to other studies where agreement ranged between 81% to 89% (146). Warshaw (2011) conducted a systematic review of teledermatology diagnosis agreement between a dermatologist following a face-to-face consultation, and a second using only photographs; providing a weighted average agreement of 65.3% (147). In a study where a similar numbers of patients were assessed (n=16) the k coefficient of dermatologist agreement was similar to our data when combining all four clinicians diagnoses(k=0.67) (119), Warshaw showed the overall k coefficient in a number of studies ranging from 0.65 to 0.87 (147).

6.11.2 Limitations

6.11.2.1 Potential limitations of participants

The population used to test the MCDTP were children attending primary care centres in South Wales and, as will be described in the subsequent subsection, the majority of this population is White British. We did not collect data of ethnicity and therefore it should be assumed the sample used to test the MCDTP may not have included children with different skin colours. This selection bias could have been reduced by testing the MCDTP in a sample of children with a range of skin colours. The features of MC are the same in children regardless of their skin colour but the usefulness of the images that were used in the MCDTP should be tested before any assumptions are made of its suitability within a more diverse population. The generalisability of the MCDTP to its target population will be described further in the next subsection.

Clinicians were provided with an information sheet describing MC that used the same key points and images as that given to parents. By providing both the parents and clinicians similar guidance for an MC diagnosis it may have meant that both were influenced in their diagnosis the same way. No information was collected from the GP as to whether they had read the information provided and, if they had, whether this guidance had influenced their diagnosis of MC, however, we found a high level of agreement between clinicians suggesting that the GPs had not been influenced when providing a diagnosis.

Only parents who responded to the study question of 'does your child have a spot, lump or bump on the skin?' were invited to participate in the study and therefore this population had a range of skin conditions that does provide the true sensitivity and specificity for conditions similar to MC.

6.11.2.2 *Potential limitations in the recording of data*

During the recording of data GPs could view the diagnosis given by the parents prior to providing their own diagnosis, as both the parent and GP diagnosis were recorded on the same page. Reading the parents diagnosis could have influence the GPs decision making. This bias could have been reduced if clinicians were blinded when giving their diagnosis, therefore ensuring they were unaware of the response given by parents. This blinding did not occur and is a limitation of the MCDTP study design. A simple improvement in the process could have been implemented by parents and clinicians recording the MC diagnosis on a different page of the MCDTP booklet, however this would not have been true blinding as clinicians could still easily access the parent diagnosis by turning the page. However, this is likely to have had little effect as GPs are familiar with making a diagnosis in the setting of an alternative diagnosis being suggested by a patient / parent.

6.11.3 *Generalisability and acceptability of the MCDTP*

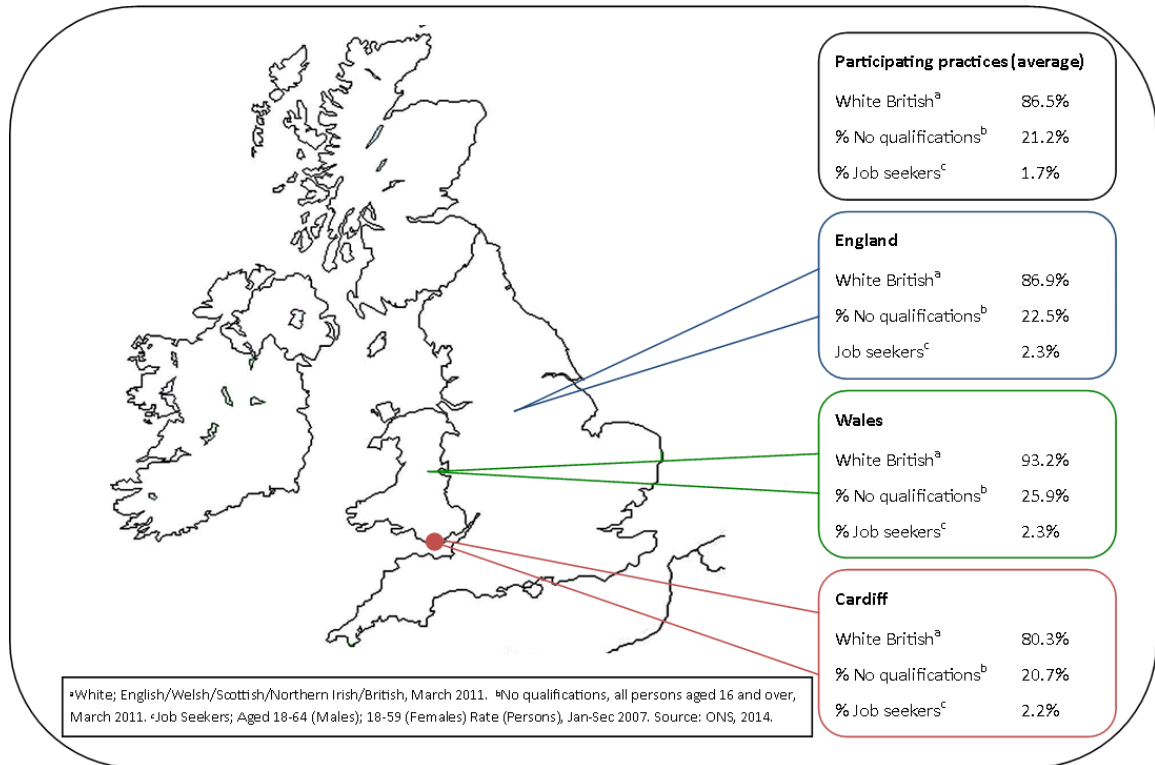
6.11.3.1 *External validity*

External validity relates to generalisability of the study findings to other populations (35). To measure the generalisability of the MCDTP it is important to seek whether there are other populations that have similar population structures for which it can be assumed the MCDTP will provide similar diagnostic accuracy statistics (35). The characteristics of general practices who participated in the research were provided earlier in Table 28. The data showed that there was a wide range of practice deprivation scores (IMD) between 1.22 to 46.72, indicating that the practices were located in areas of both high and low relative deprivation, and suggests that study participants provide a range in their socio-demographics characteristics. All of the practices were classed as being located in 'urban' areas and therefore rural areas were not represented within the population which is a limitation of this study.

There is a risk of selection bias which would mean that the sample population are not similar to the general population, however we do not feel this was a problem because the characteristics of our study population appear to be similar to the general population. For example when further comparisons of the data are made to the populations of Cardiff, Wales and England (Figure 21) the percentage of the participating practice populations being recorded as White British ranged between 59.5% to 95.4%, and provided an overall mean value of 86.5%, this figure is comparable to England (86.9%), however lower than the Welsh average (93.2%) (142). Further comparisons are presented in Figure 21 which indicates that the practices who participated in the study were comparable to that of England and Wales using these three general measures (Figure 21 highlights the percentage of the working age population with qualifications, percentage of the population receiving Job seekers allowance (JSA) and ethnicity; these measures were chosen as qualification status can be an indicator of health literacy (148), the percentage receiving JSA can be an indicator of levels of deprivation within a population (149), and the percentage of the population classed as White British is an indicator of ethnic diversity).

It is important to highlight that the demographic data of the sample is based upon the local data relating to the practice postcode (Lower Super Output Area (LSOA)) and not individual participant characteristics, however as individual practice characteristics are not available this is the best data available for this comparison.

Figure 21. Characteristics of sample, English, Welsh and Cardiff populations



6.11.3.2 Features to improve the external validity

Elements of a study design can reduce the external validity of findings such as limiting the eligibility of those who can participate in the research (150). To avoid this, an inclusive recruitment plan was implemented in this study. All practices within Cardiff and Vale were invited to participate in the study (n=93), of those practices within Cardiff 12 responded and this group of practices participated in the research. Within the practices recruitment was active for over eight months where all potentially eligible parents visiting the practice were invited to participate in the study. Study materials were limited to only being available in English, and therefore this language barrier may have unavoidable excluded some potential participants from taking part in the study.

6.12 Conclusions

The data suggest the MCDTP is suitable for use in an epidemiological study and the population used to test the MCDTP are shown to be generalisable to other populations in the UK. Therefore, the MCDTP is suitable for use as a recruitment tool in the following chapter (seven).

Chapter seven: Prospective cohort study of children with molluscum contagiosum

An original research article was published in *The Lancet Infectious Diseases* describing time to resolution, transmission and impact on QoL of MC in children. A copy of the published manuscript can be found in Appendix 1.3.

7. Overview

This chapter will describe the design, setting, procedure, and results of a prospective cohort study of children with MC. The chapter will conclude with a summary of the findings and discuss potential limitations of the study.

7.1 Background

Data on the epidemiology of MC is generally of poor quality. There is little data on the time to resolution of the condition, and there have been no studies which have described the presentation, management, transmission between siblings and impact on QoL in a large community cohort of children living in the UK.

Measuring QoL for dermatological conditions is particularly important, and although skin conditions are not generally life-threatening they can have a major impact on patients' psychosocial state, social relationships and everyday activities (151). By measuring QoL the effects of disease from the perspective of the patient or child can be ascertained (73).

7.2 Study Design

This is a prospective cohort study of children recruited from the community with MC.

7.3 Rational for study design

The prospective cohort design is useful for estimating causal relationships between exposures (e.g. age, sex, treatment) and subsequent outcomes (e.g. time to resolution) (30). The design does have limitations. Recruiting a cohort and following-up participants for the duration of

symptoms can be expensive, and cohort studies are subject to loss of study participants (152). However, this can be factored into the sample size to ensure enough study participants are recruited to provide significant power for potential participant drop-out (153). The management of the study can be amended to use techniques that are quick and simple to allow participants to provide follow-up data, and maintain engagement with the study. For a condition, such as MC, where cases infrequently report to primary care, there can be difficulties in recruiting a sufficient number of cases from only this setting (152). Where participants are recruited from the community and recruitment is not limited to only primary or secondary care centres, it is possible for a larger number of cases to be recruited without needing a substantial amount of primary care sites to recruit, which can be logistically difficult and expensive. Additionally, recruiting only from primary or secondary care centres can introduce bias to the study results whereby it can limit the generalisability of the findings as it includes only the health care seeking population, and possibly more severe cases (27). By recruiting from a larger footprint and reaching out to recruit from both health care centres and the community, through a range of novel techniques, the findings from this study will be more representative of children living in the UK than if only children attending health centres were recruited.

Other study designs could have been used such as a retrospective cohort or case series study. The retrospective study is recommended when the objectives are to determine the incidence and time to resolution of a condition (154), as are the objectives for this study. The benefit of a retrospective cohort design are that generally the data are already collected from other sources and all that remains are gaining access to data and analysis. However, as the data are already collected it does not allow for additional information to be captured or for patients to be followed to describe outcomes, also, often this data are collected from the health care setting meaning the data may not be representative of cases in the community. A second alternative design was a case series; this is a descriptive study design that can provide the clinical

description of a disease and recruits a large number of patients with the disease for this purpose (155). Data from patients are captured at one point in time which distinguishes this design from a cohort study where data are collected for patients at different time points (41). If data from patients is captured to describe previous symptoms it relies upon accurate parental recall and this may cause a reduced reliability of results (156).

To allow for the prospective follow-up of participants, unique data to be collected and to ensure the sample was representative of children in the both the community and health setting, both the retrospective cohort and case series study designs were dismissed in favour of the prospective cohort design for this study.

7.4 Objectives

The primary and secondary objectives of this study were;

7.4.1 Primary objectives

- Determine the time to resolution of MC lesions.
- Describe the reported transmission of MC in the children living in the same household as a primary case.
- Describe the impact of MC on quality of life.

7.4.2 Secondary objectives

- Describe the symptoms of MC in children aged four to 14.
- Describe the management of the condition by both clinicians and parents, including prescribed and non-prescribed therapies.
- Describe prevalence of other skin conditions presenting in children prior to their current MC diagnosis.
- Describe prevalence of risk factors, such as contact sports.
- Describe the impact of MC on day to day activities, mood and relationships.

7.5 Population

The target population were children, aged four to 14, with a current diagnosis of MC. The diagnosis was confirmed by either a clinician (during a consultation) or following completion of an online version of the 'MCDTP'.

7.5.1 Setting

Patients were recruited using three main sources a) General practices, b) Dermatology outpatient clinics, and c) Media advertising and social media.

7.6 Recruitment processes

7.6.1 General Practices and Dermatology outpatient clinics

Children with MC were recruited from general practices and dermatology outpatient clinics which acted as participant information centres (PICs). Parents of children who were diagnosed with MC, either during a clinical assessment or when completing the 'MCDTP' during the validation study (chapter six), were invited to participate in the study. If a parent or guardian wished to participate they were asked to complete a study information card whilst in the clinic. The information card recorded the parent's name, telephone number and email address (Appendix 4.3). Once completed, parents were asked to leave it with the practice receptionist who returned it to myself. Once I received the study card I contacted the parents and directed them to the study website to complete the questionnaires or sent a paper questionnaire by post if this was their preferred option.

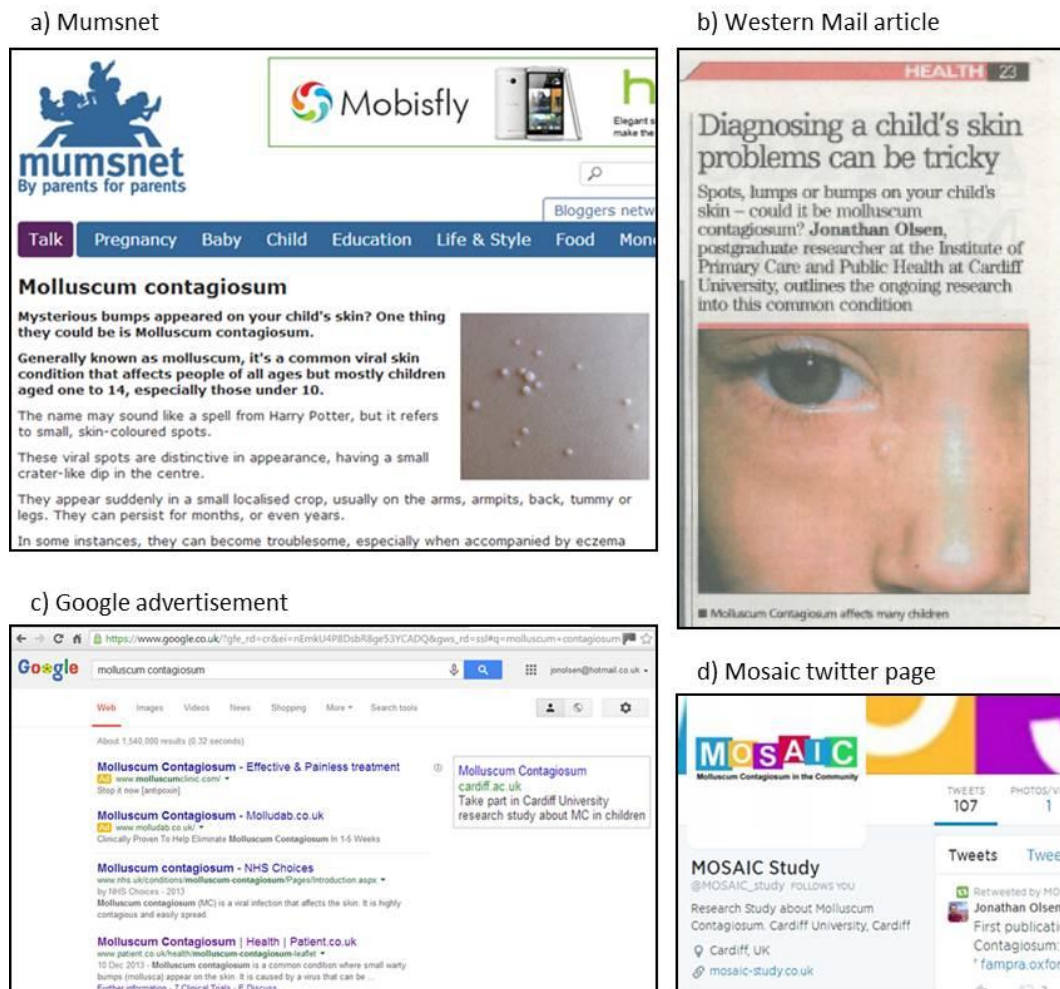
7.6.2 Media Advertisement

Participants were recruited through a media awareness campaign which published information about the MOSAIC study. Published articles provided brief information about the study and directed potentially eligible participants to the MOSAIC study website. Once at the website, parents were asked to read the study materials, provide consent, and complete the online

version of the 'MCDTP'. Only parents who diagnosed that their child currently had MC using the MCDTP were invited to join the study.

To construct an effective process for the distribution of information for the mosaic study, a meeting was arranged with the Cardiff University press relations (PR) team. PR officer, Tom Barrett, provided advice describing the best methods to raise awareness of the study from his experience; advising that to gain good coverage of the study in local news outlets it would be beneficial to provide a press release. The recruitment methods will be described in detail below and examples of these methods are shown in Figure 22.

Figure 22. Examples of recruitment and study awareness methods



7.6.2.1 Local media

A 'press release' was distributed to local news outlets by the Cardiff University PR team that provided text for a print or online article. This article provided information about MC in children, briefly summarised the 'MOSAIC study', and directed parents to the MOSAIC website if they wished to participate in the study, or if they wished to receive more information about the study.

A short article was published in the 'Western Mail' on Monday 15th April 2013 entitled 'Diagnosing a child's skin problems can be tricky: Spots, lumps or bumps on your child's skin - could it be molluscum contagiosum?' (Figure 22b) (157). The Western Mail is a daily Welsh national newspaper with a distribution of 32,926. A copy of the article text and a scanned version of the print version are in Appendix 4.4.

7.6.2.2 Health forums

Information about the study was posted on two health forum websites 'mumsnet' and 'netmums' (Health forums are independent websites that provide an online network for parents where they can post and share parenting information (158)). The same text was posted on each site and uploaded to the section for non-member requests. Posting a 'non-members request' on mumsnet incurred a charge of £30 and posting on netmums incurred no charges.

Both websites contained a mini encyclopaedia of common diseases in children and neither contained a page providing parents with information about MC. I contacted both website editors to discuss providing additional content about MC which could be posted in their disease encyclopaedia section. Both of the website editorial teams responded, Netmums noted my email, stating that for the moment they would not be providing an information page about MC. Mumsnet responded positively to adding an information page for MC, and in the following months posted an information page based on information I supplied

(<http://www.mumsnet.com/health/children/molluscum-contagiosum>) (Figure 22a). The MC information page on 'mumsnet' included a direct link to the MOSAIC study website for parents whose child had MC or they wished to use the MCDTP to diagnose a skin lesion. The link to the MC information page on mumsnet was also included within their weekly email newsletter sent to members on 25/04/2013.

7.6.2.3 Social media

Two specific social media accounts were created for advertising of the MOSAIC study on Facebook and Twitter; Table 34 highlights the relevance of these social media tools for health professionals and researchers.

Table 34. Social media tools and relevance to health professionals or researchers

Social media tool	Relevance to health professionals or researchers
Facebook	Global social networking site contains over half a billion members and increasing numbers of health professionals, medical organisations, illness-based support groups, and medical journals using this to share health information.
Twitter	Free microblogging platform in which over 100 million users worldwide—including health professionals, patients, and members of the lay public—publish brief text-based posts of up to 140 characters on their profile pages to alert others to what they are doing, thinking, reading, or writing in the moment. Can be used to track real-time information flow about topical health issues.

Table adapted from George (2011) (159)

Facebook

Using Facebook, a 'page' was created to provide information about the research study; an advert was developed to direct users to this page.

Posting adverts on Facebook incurred a charge; this charge was based on the number of people who 'clicked' the advert, and whether this 'click' occurred at peak or off-peak times. The advert presented on the right hand side of the web browser while Facebook users were logged into the website. Facebook hold information of their users such as age, location, computer being used, and age of children (if user has a child). Within the Facebook advert

application a defined criteria was created to limit the scope of the advert to show only to selected users and ensure only those who may be eligible to take part in the study could view the advert therefore limiting the number of irrelevant 'clicks' and cost to the study. The criteria for the advert were:

- Male or Female
- Aged 18 to 55
- Resident of the UK
- Using a desktop computer
- Has a child aged four to 14 years.

Once parents 'clicked' on the advert they were directed to the study website. A total of 60,403 impressions (advert appearances) were made when a Facebook user was online and met the advert criteria. From these impressions on internet browsers, 25 parents clicked on the advert directing them to the MOSAIC study website. The total cost of advertising using Facebook was £43.28 (\$71.39 converted on 24/03/2014 using google currency calculator).

Twitter

A twitter account for the study was launched in March 2013 using the name '@MOSAIC_study', the purpose of this account was to provide information about the study to users of the social network (Figure 22d). At the study close date (31/07/2014) the account had a total of 222 'followers'. The account was used as a mechanism to distribute short informative text to potential study participants and provide a link to the MOSAIC website. The administrator of a widely used twitter account (4,607 followers) providing information to parents and academics about eczema, the Nottingham Eczema support group (@eczemasupport), was contacted to ask if they would inform their followers of the MOSAIC study. The Nottingham Eczema group informed their followers on 14 separate occasions about the MOSAIC study.

The number of participants who clicked on the website following notification of the study from twitter is unknown, and therefore measuring the success of this is difficult.

7.6.2.4 Google advertisement

Google is the largest search engine in the UK, accounting for 90% of all searches made from a desktop computer (160). Adverts can be placed on the search engine using google 'Adwords'. Google adverts are related to the search terms entered by a user and given a prominent position at the top or side of the page distinguishing them from the main search results. An advert was created when UK users of google entered specific search terms about MC. The text within the advert was limited to 25 characters for the title, and 70 characters within the main text. The final advert text was "Mollusum Contagiosum: Take part in Cardiff University research about MC in children" (Figure 22c).

The advert was shown once a user provided specific search terms (Table 35), google users could click anywhere on the advert and this would open a new web browser containing the MOSAIC study website. Each time the advert was clicked a cost was incurred, the cost of each click was based upon google analytics modelling which factored whether it was at peak or off-peak times. Overall the advert made 167,181 impressions following a search, and was clicked 492 times. The total cost incurred for these clicks was £328.55.

Table 35. Search terms for Google 'Adwords'

Mollusum	Mollusum Contagiosum child
Mollusum Contagiosum	Mollusum Contagiosum treatment in children
Mollusum Contagiosum Children	Get rid of mollusum
Mollusum in Children	Mollusum in kids
Children Mollusum	Mollusum Contagiosum treatment children

7.6.3 Schools

Local schools in Cardiff and Swansea were emailed information about the MOSAIC study; the email contained a letter containing information about the study. If schools wished to

participate in the study by sending letters to parents they were asked to contact myself for the documentation to send. Parents of children who attended participating primary schools were then sent letters home either by hand or via an email to parents. The letters informed them of the study, what it involves and what to do if they would like to receive more information. Those who wished to receive more information about the study were either directed to the MOSAIC study website or were provided with my Cardiff University email address to contact me directly.

One school responded to confirm they had forwarded this email to their parent distribution list; however other schools forwarded the email without notifying myself. I was notified of emails being sent from schools when parents emailed me directly to ask for information about the study. Primary schools in Cardiff (n=95) and Swansea (n=62) were emailed on 21/05/2013 and 24/06/2013 respectively. The success rate of informing parents of the study through schools cannot be determined, as the denominator of how many parents were contacted is unknown.

7.6.4 Recruitment timetable

Table 36. Recruitment timetable by different methods

Recruitment	2013									
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct
Diagnosis confirmed by clinician										
GP surgeries recruiting from MCDTP validation										
Dermatologist referrals in Welsh outpatient department	IRAS amend	R&D Approval								
Diagnosis confirmed using MCDTP										
Media recruitment (Western Mail article)										
Online health forum / discussion board advertisement										
Social Media (twitter/facebook)										
Google Ad words										
Schools										

Recruitment of participants who had an MC diagnosis confirmed by a GP commenced in January 2013 at GP practices taking part in the validation of the MCDTP (Table 36). Within the original ethical approval dermatology clinics were not included as sites for recruitment; however an amendment was submitted to the ethics board, subsequently approved and dermatology clinics began recruitment in March 2013. Referral to the study using the MCDTP commenced in April 2013 once the MCDTP had provided sufficient accuracy in parental diagnosis. Recruitment ended in October 2013 allowing follow up of participants to August 2014 (study end date).

7.7 Procedure

Participants completed a structured questionnaire about the presentation, burden of disease, advice, and the CDLQI at recruitment to the study. To describe the time to resolution of symptoms and transmission to other family members' participants were followed up via text message or email until lesions had cleared, or the study period had ended.

7.7.1 MC Questionnaire

The MC Questionnaire was purposefully designed for this study to collect information from the participants that would fulfil the outcomes of the study. Information was collected to provide data of the following key areas;

- Demographics: Age and gender.
- History: Duration, number and site of lesions, previous skin conditions.
- Treatment: All prescribed and non-prescribed treatments for MC that had been used.
- Risk factors and transmission: Participation in sports activities, other children within household and whether they have had MC.
- Diagnosis and advice: Whether diagnosis was confirmed by a doctor, whether they had received advice and information from the doctor and whether they had received information from other sources.

A copy of the questionnaire can be found in Appendix 4.1.

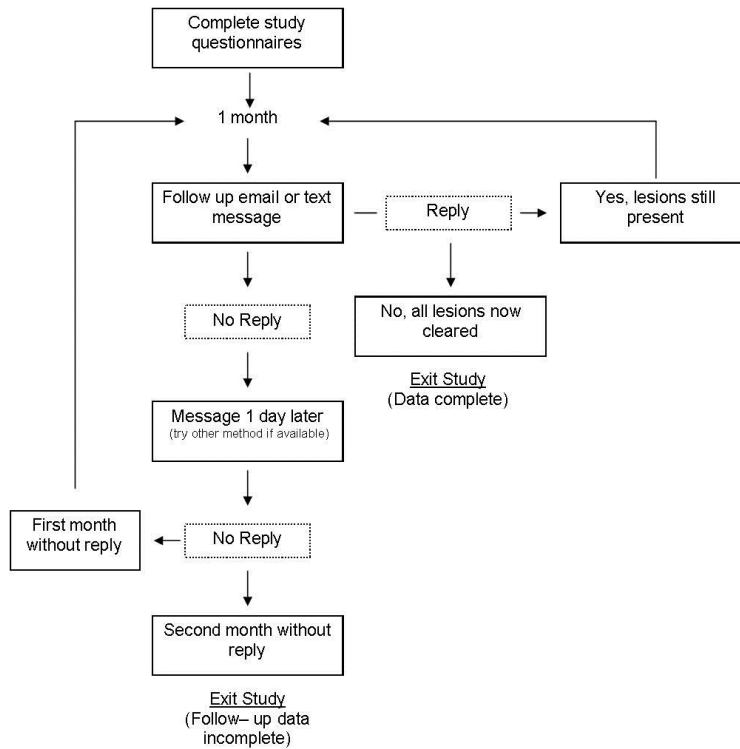
7.7.2 Time to resolution and follow-up

A primary outcome of this study was to describe the time to resolution of symptoms. Data describing the time to resolution of the condition was captured prospectively by the follow-up of participants, this also collected data on whether there had been further instances of transmission between other children within the family since completion of the original questionnaire.

Participant Follow-up Procedure

An excel spreadsheet was developed containing follow-up information about the study participants. Contact details were obtained from the final page of the MC questionnaire where participants provided an email address and/or telephone number. Emails were sent from the following Cardiff University email account – olsenjr@cardiff.ac.uk. A study mobile telephone was purchased for the specific purpose of sending follow-up text messages; this phone, when not in use, was located within a locked draw of a secure building at Cardiff University. This phone was not used for any other purposes other than this study to ensure confidentiality of participant personal data.

Figure 23. Text message and email follow-up procedure



Each participant was sent an email and/or text monthly with the text “Please could you answer the following monthly follow-up questions? 1) Are your child's skin lesions still present? 2) Have any siblings developed Molluscum Contagiosum? Please reply to this email/text” (including one reminder) (Figure 23), if on two consecutive months there was no reply, the participants were not contacted again and marked in the database as ‘non respondent’.

7.7.3 CDLQI

The CDLQI is the most widely used dermatology specific QoL measure for children with dermatological conditions (67, 69). The questionnaire consists of 10 questions to establish impact upon quality of life around the following areas:

- Symptoms and feelings
- Leisure
- School or holidays
- Personal relationships
- Sleep

- Treatment

A copy of the CDLQI can be found in Appendix 4.2.

7.8 Data management

In order to facilitate ease of use by as many different participants as possible a hybrid system using both postal and online data collection was used for collecting study data. Combining these methods provided more opportunities for participants to take part in the study and by including an electronic survey it had the ability to improve response rates (161).

7.8.1 GP/Dermatology referrals

Questionnaires were posted to participants who were referred from the study following a positive MC diagnosis by a GP/dermatologist as well as being able to complete the survey online. Participants were provided with a stamped addressed envelope to return the completed forms. Returned questionnaires were uploaded using a purposely designed form into IBM SPSS Data Collection Interviewer v6.0.1. The data was exported as a 'sav' file, and converted into a 'dta' file for analysis in STATA v12.

7.8.2 Web referrals using MCDTP

Participants referred to the study via media advertisement were able to complete questionnaires online via www.mosaic-study.co.uk. As the data collected included patient sensitive and identifiable information a secure website was required. The website was designed and managed by the web development team (healthy ageing research group), Institute of Primary Care and Public Health, Cardiff University. The website followed the same questions and format as the paper questionnaire. Data was exported into a secure excel file and sent to myself when requested.

7.8.3 Merging databases

A password protected master file was created which contained merged data from the web recruitment tool and the data from the paper forms. Each field was individually checked to

ensure that the coding was the same for each response before exporting into a STATA data file. Each participant was assigned a unique study ID, a separate spreadsheet containing only follow-up details was created for use in the monthly follow-up text messages and emails.

7.9 Outcomes

7.9.1 Sample size calculation

The main outcomes of the study were to provide descriptive statistics of differences between groups and proportions following the completion of the two study questionnaires (MC questionnaire and CDLQI).

Formula:

$$n = \frac{Z^2 P(1 - P)}{d^2} = \frac{1.96^2 0.05(1 - 0.05)}{0.025^2}$$

Where:

n = sample size

Z = Z statistic for level of confidence

P = expected prevalence or proportion

d = precision

Sample size calculation based on Naing et al (2006) (162)

The sample size calculation (formula above) was based upon ensuring a representative sample of MC cases were recruited which described a range of children with varying presentations of the condition. No recent studies have described the prevalence of MC in the community for children in the UK or Northern America and therefore estimating the true prevalence of MC for the sample size calculation required assumptions.

The meta-analysis presented in chapter two provided a combined overall estimated prevalence of MC in children as between 5.1% to 11.5%. Using an expected prevalence of MC in the community as 5.1% resulted in a sample size of 292 participants (as the prevalence estimate was less than 0.1 the precision used in calculation was half of the expected prevalence (d=0.025), as recommended (162)). Assuming a prevalence of MC as 11.5% resulted in a sample of 162 using a 95% confidence interval and a precision of 0.05. To ensure

an adequate sample of children were recruited to provide accurate precision of 0.025 in a proportion of one, with a level of confidence of 95% and estimating a cautious lower estimate of MC in the community of 5.1%, a minimum sample of 292 children was required.

7.9.2 Analysis

7.9.2.1 MC Questionnaire

Descriptive statistics were calculated for all outcomes. Distributions were described using the mean and / or median and the standard deviation (SD) and / or the first and third quartiles (Q_1 and Q_3) and / or the range, depending on the distribution. Time to resolution is measured by the number of months in total that the lesions were present; the event start date was the date lesions were initially present and resolution measured as the point lesions were no longer visible. Survival estimates were calculated using Kaplan-Meier statistics. Hazard ratios show whether gender, having an affected family member, treatment (prescribed / non-prescribed) or a greater number of lesions impact on the time to resolution. Data from participants lost to follow-up were censored at the first incomplete follow-up time point; data for those who had not recovered by the end of the study were censored at the study end date. Transmission analysis (as a proportion) between family members was limited to only those living with family members aged under 14 years. Statistical analyses were performed within STATA v12.

7.9.2.2 CDLQI

Each response was given a score based on standard guidelines for the CDLQI (shown below) (67, 71) where each question is scored, these individual scores are then counted to provide an overall CDLQI score. A histogram of CDLQI scores was plotted to describe the distribution of data, the data from the CDLQI scores are positively skewed and no transformation was adequately able to improve the fit of normality, so a non-parametric Kruskal-Wallis test was conducted to compare the medians for the predictor variables with two or more levels. The

overall mean, standard deviations and medians (Q_1 and Q_3) of CDLQI scores were calculated based upon individual question responses. The scoring for each question is;

- Very much = 3
- Quite a lot = 2
- Only a little = 1
- Not at all = 0
- Blank = 0
- Q7 – Prevented school = 3

7.10 **Results**

A total of 306 parents completed the study questionnaire between January and October 2013 (Figure 24). Recruitment numbers were highest during May, June and July where health forum information was placed, letters had been sent to schools and google advertisement was active. 90.5% of participants were recruited by self-diagnosis using the MCDTP via the study website, 9.2% were referred to the study following a diagnosis from primary care, and one participant was referred from a dermatology outpatient clinic. Figure 25 shows the recruitment of participants through each campaign.

Figure 24. Monthly recruitment of study participants

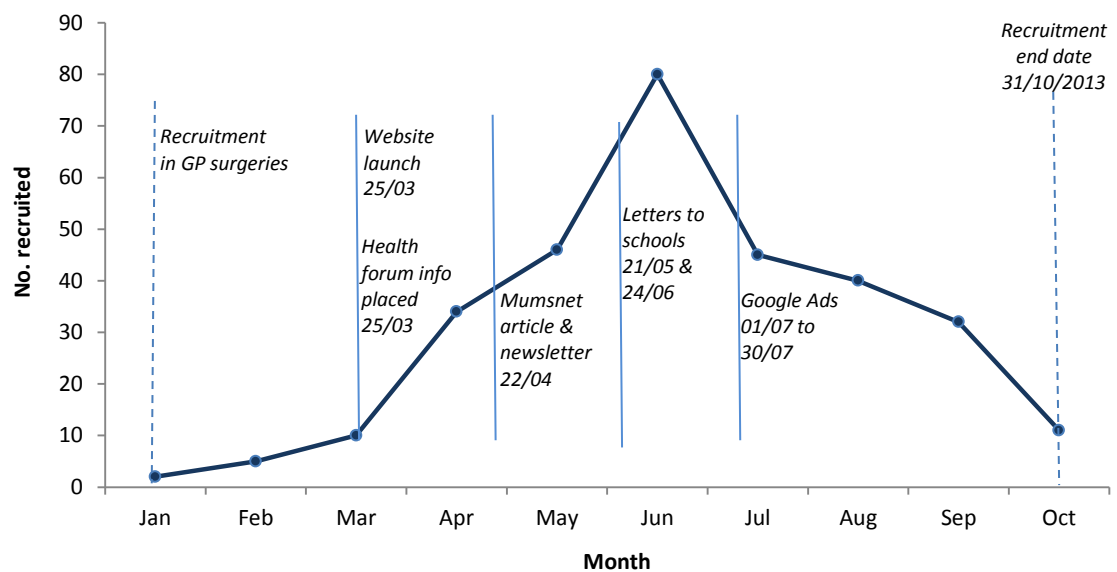
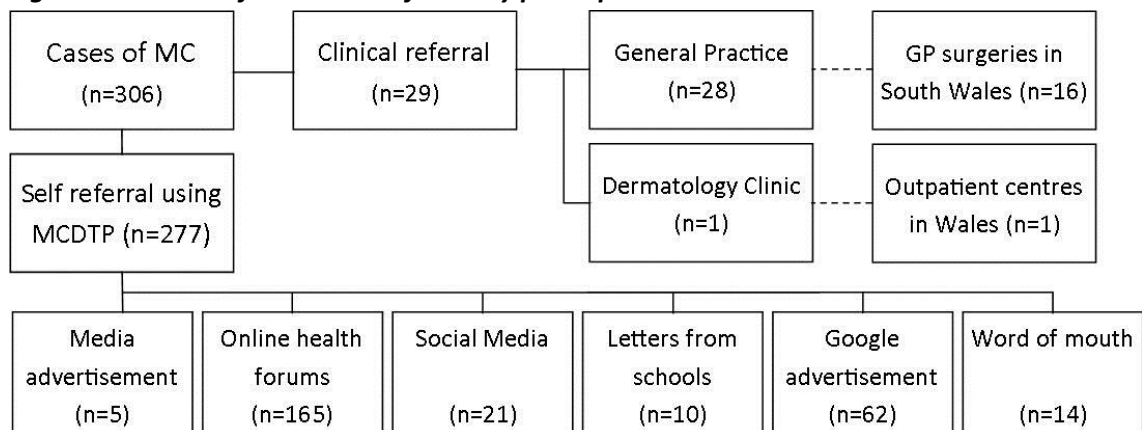


Figure 25. Source of recruitment for study participants



7.10.1 Participant Characteristics

The age of children ranged from four to 15 years, and the median age was positively skewed with a median (Q_1 , Q_3) of 12 (5, 8). There was an even distribution between the genders (45.4% male). Participant characteristics are described within Table 37. In most cases children had more than one lesion, and 56.8% had more than 10. In a quarter of cases there were over 21 lesions present (Figure 26). The most common anatomical location of lesions was legs (51.3%), torso (49.7%), and arms (49%). 69.6% of children had lesions in more than one site (Figure 27), the most common pair of locations were torso and arms (32.4%). Figure 28 provides an

illustration of the most common anatomical locations of lesions using data for all children included in the sample.

Table 37. Participant characteristics

i) Participant characteristics (n=306)			
a) Age (years)			
	Mean (SD)	6.7 (2.4)	
	Median (Q_1 to Q_3)	6 (5 to 8)	
	Range	Min=4, Max=15	
b) Gender			
		Number of participants	%
	Male	139	45.4
	Female	167	54.6
ii) Presentation			
a) No. of MC lesion/s present			
		Number of participants	%
	1	21	6.7
	2-5	55	18.0
	6-10	56	18.3
	11-15	48	15.7
	16-20	50	16.3
	21+	76	24.8
b) Location of lesion/s (multiple responses available)			
		Number of participants	%
	Legs	157	51.3
	Torso	152	49.7
	Arms	150	49.0
	Armpits	69	22.5
	Back	62	20.3
	Genitals	53	17.3
	Buttocks	51	16.7
	Face	49	16.0
	Neck	47	15.4
	Hands	13	4.2
	Feet	12	3.9
	c) Most frequent pairs of locations		
		Number of participants	%
	Torso and arms	99	32.4
	Torso and legs	86	28.1
	Arms and legs	75	24.5

Figure 26. Number of lesions present by participant at point of survey completion

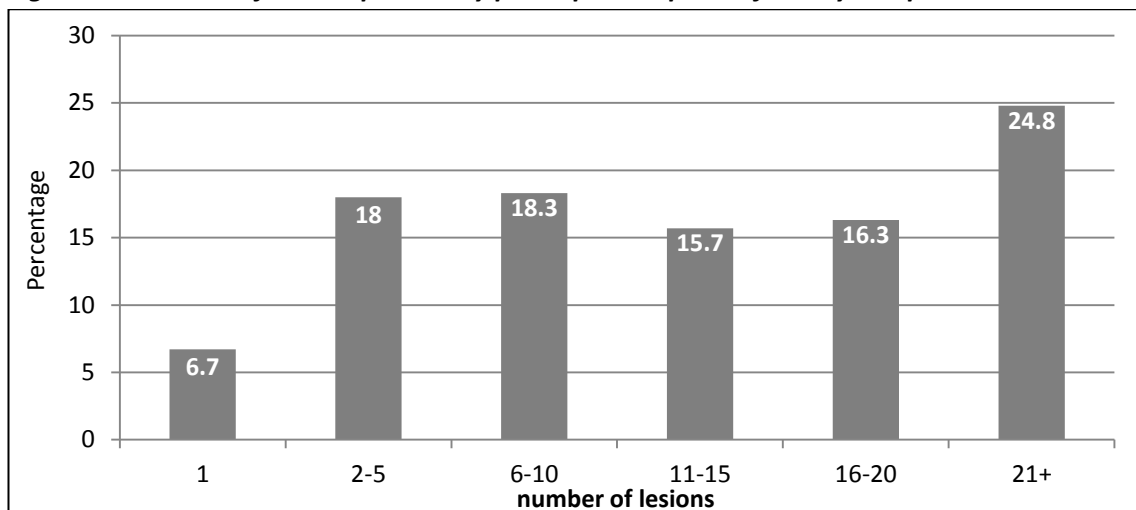


Figure 27. Number of anatomical sites MC lesions present

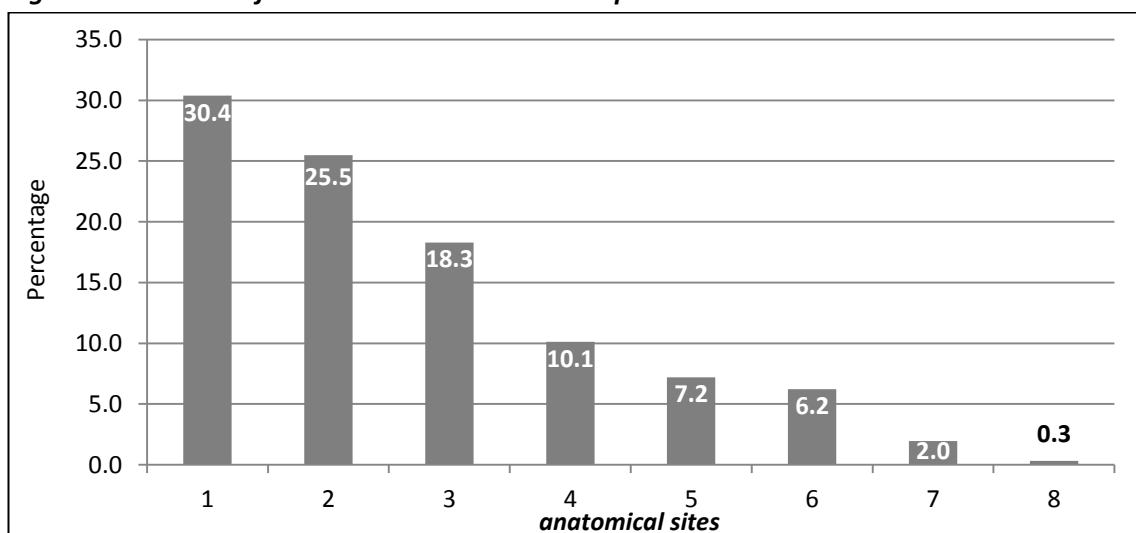
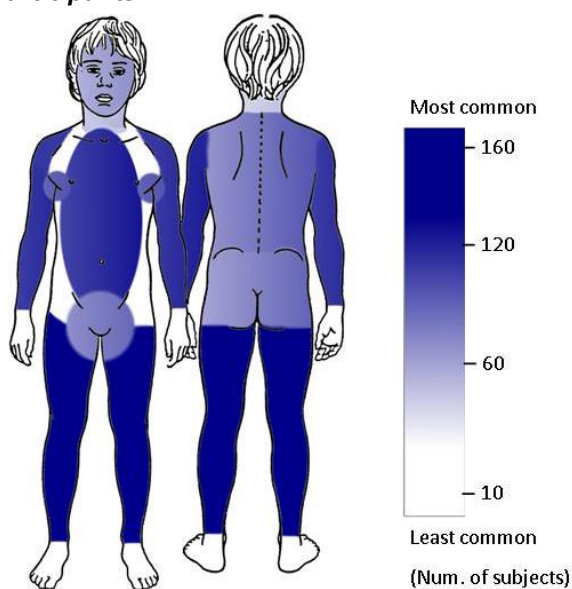


Figure 28. Distribution of lesions by anatomical site and frequency of presentation in study participants



7.10.2 Treatment and Advice

81.1% (n=248) parents indicated that they had visited their doctor for advice about their child's MC (Table 38). Figure 29 highlights the information parents recall being given during their child's MC consultation. In 92.7% of cases a clear description of the disease was provided, and in most cases this was provided verbally (83.9%), in 15.7% of cases the parents were provided with printed information sheet about MC.

Table 38. Treatment & Advice

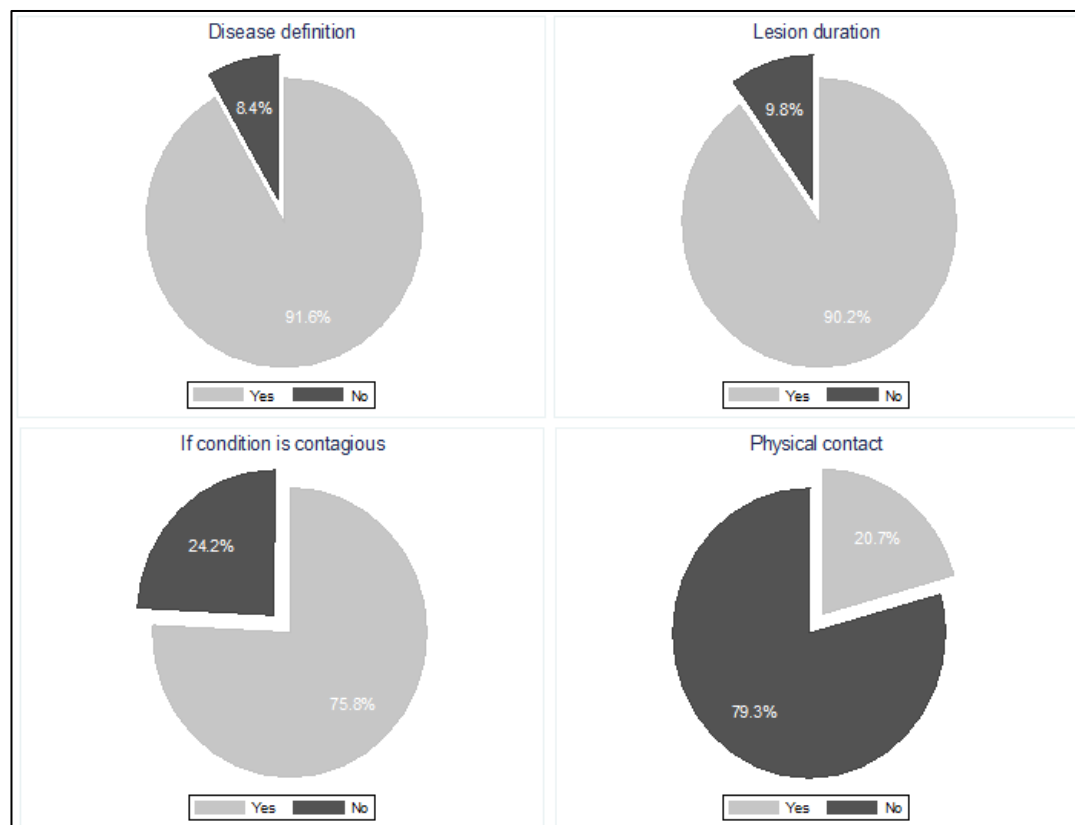
a) Has your doctor confirmed a diagnosis of MC			
		<i>Number of participants</i>	<i>%</i>
	Yes	248	81.1
	No	58	18.9
b) Did your child receive any treatment from the doctor?			
		<i>Number of participants</i>	<i>%</i>
	Yes	58	23.4
	No	190	76.6
If yes, what treatment?			
	Treatment	<i>Number of participants</i>	<i>%</i>
	Antibiotic	18	31.0
	Topical ointment	31	53.4
	Steroid cream	3	5.2
	Antihistamine	2	3.4
	Curettage	1	1.7
	Molludab	1	1.7
c) Did you use alternative treatments not prescribed by the doctor?			
		<i>Number of participants</i>	<i>%</i>
	Yes	121	39.5
	No	185	60.5
If yes, what treatment? (1 blank response)			
	Moisturising lotion	21	17.4
	Cutting or squeezing	16	13.2
	Use in one or less cases	83	68.6
d) Did seek advice from anywhere else?			
		<i>Number of participants</i>	<i>%</i>
	Yes	167	54.6
	No	139	45.4
If yes, where did you seek advice?			
	Internet	144	86.2
	Healthcare practitioner	16	9.6
	Friends	7	4.2

The time to resolution of lesions was described to parents in 88.7% (n=220) of cases when they saw the doctor. Parents were told lesions would resolve by up to 12 months (28.2%), up to 18 months (31.4%), up to 24 months (20.5%), and over 24 months (3.6%). 28 parents (12.7%) were provided information about the time to resolution but did not state what information they were given.

Parents were told in 57.3% that the lesions were contagious, 24.9% were told that their children should take measures to avoid transmission; however 7% of parents reported being told that MC was not contagious.

In 20.2% of consultations parents noted that physical contact was discussed. In most cases (38%) parents reported being told that their child should continue all activities as normal. 26% reported being told to avoid skin to skin contact and 22% were told not to share towels. In 4% of consultations parents were told that their child should discontinue with school swimming activities.

Figure 29. Advice received from GP (when participant saw doctor)



7.10.3 Associations with other skin conditions

A third of participants (34.6%) reported that their child had another skin condition present in the months prior to developing MC (Table 39). In almost a quarter of children there was a prior diagnosis of AE. Other skin conditions were noted but these were present in less than 1% of cases.

Table 39. Association with other conditions

a) Other skin conditions present in the months prior to developing MC			
		<i>Number of participants</i>	<i>%</i>
	Yes	106	34.6
	No	200	65.4
b) if yes, skin conditions named			
	Area	<i>Number of participants</i>	<i>%</i>
	Atopic eczema	86	28.1
	Warts	3	0.9
	Chicken pox	3	0.9
	Vitiligo	2	0.9
	Impetigo	1	0.3
	Measles	1	0.3
	Other	10	3.3

7.10.4 Activities

A quarter of children (24.8%) with MC participated in sporting activities (Table 40).

Table 40. Sporting activities

Table 4: Sporting activities			
a) Participation in sporting activities			
		<i>Number of participants</i>	<i>%</i>
	Yes	76	24.8
	No	230	75.2

7.10.5 Transmission

Of the total number of participants, 81.7% (n=250) of participants reported that there were more than one child aged 14 and under living in the same household. Of those with multiple children living in the same household 41% (n=102) indicated that there had been multiple cases of MC within the household. Transmission included occurrences both prior to (documented on MC questionnaire) and during follow-up.

7.10.6 Time to resolution

Complete follow-up data were available for 269 (87.9%) children, with 21 (7.8%) of these patients not recovering by study end (August 2014). The remaining 16 (5.2%) were lost to follow-up (no response to follow-up email/text in two consecutive months). Data where participants exited the follow-up or lesions had not cleared by the end of the follow-up period were censored for the purposes of data analysis. For those with complete follow-up data, the time to resolution was a median (Q_1 , Q_3) of 12 (8, 18), mean (SD) of 13.3 (8.2) months, and a range of 1 to 62 months (Table 41). 58.0% of children having recovered by 12 months, 29.7% still with lesions at 18 months, and 13.4% with lesions persisting at 24 months.

Table 41. Time to resolution of MC lesions

Statistic	Months
Mean (SD)	13.3 (8.2)
Median (Q_1 to Q_3)	12 (8 to 18)
Range	Min=1, Max=62

A Kaplan-Meier plot of time to resolution, including censored data, showed no difference by gender (Hazard ratio: 1.06: 95% CI 0.84 to 1.35, $p=0.617$) (Figure 30). There were no associations between the time to resolution and self-reported receipt of prescription medication, self-medication, having an affected family member or a greater number of lesions at recruitment ('21+') (Table 42, Kaplan-Meier survival estimates for these groups are presented in Appendix 4.5). However, there was a difference in the time to resolution between those who self-referred (mean 8.9: 95% CI 6.4 to 11.4 months) and those that were referred by a clinician (mean 13.3: 95% CI 12.3 to 14.2 months) (Hazard ratio: 0.58: 95% CI 0.34 to 0.98, $p=0.40$).

Figure 30. Kaplan-Meier survival estimates of lesions (in months) by gender

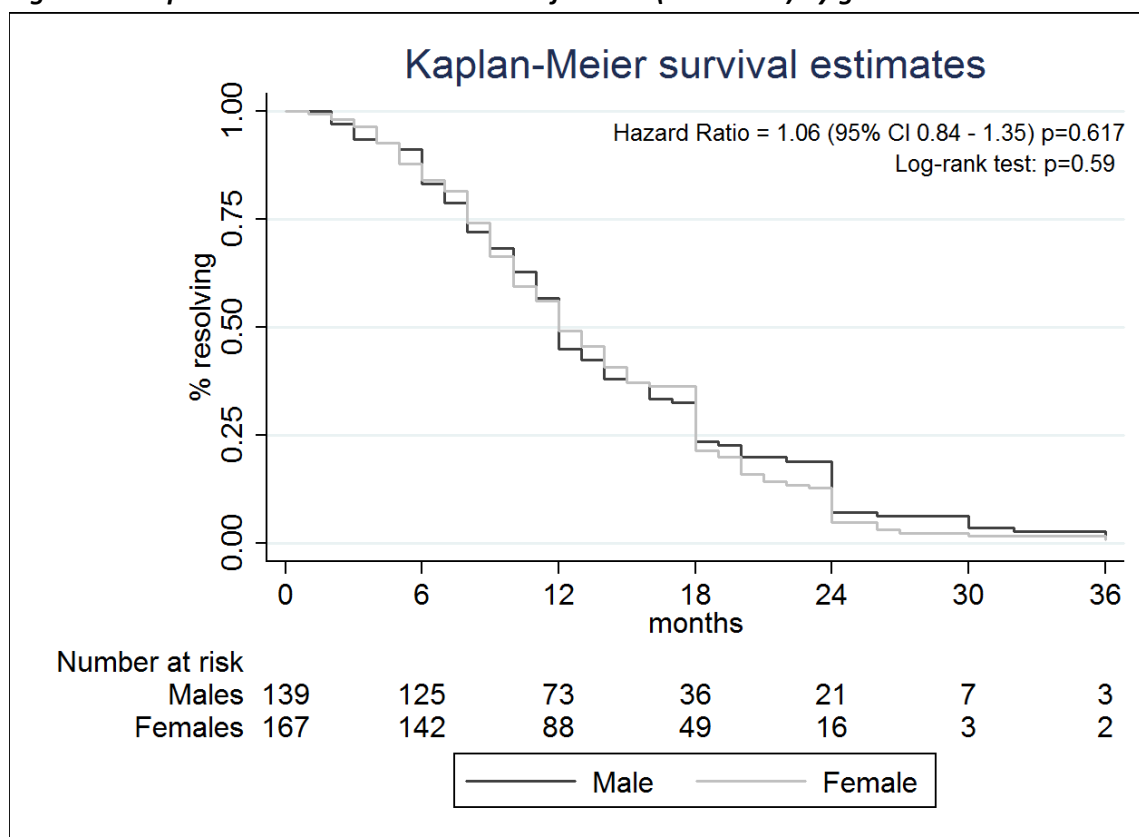


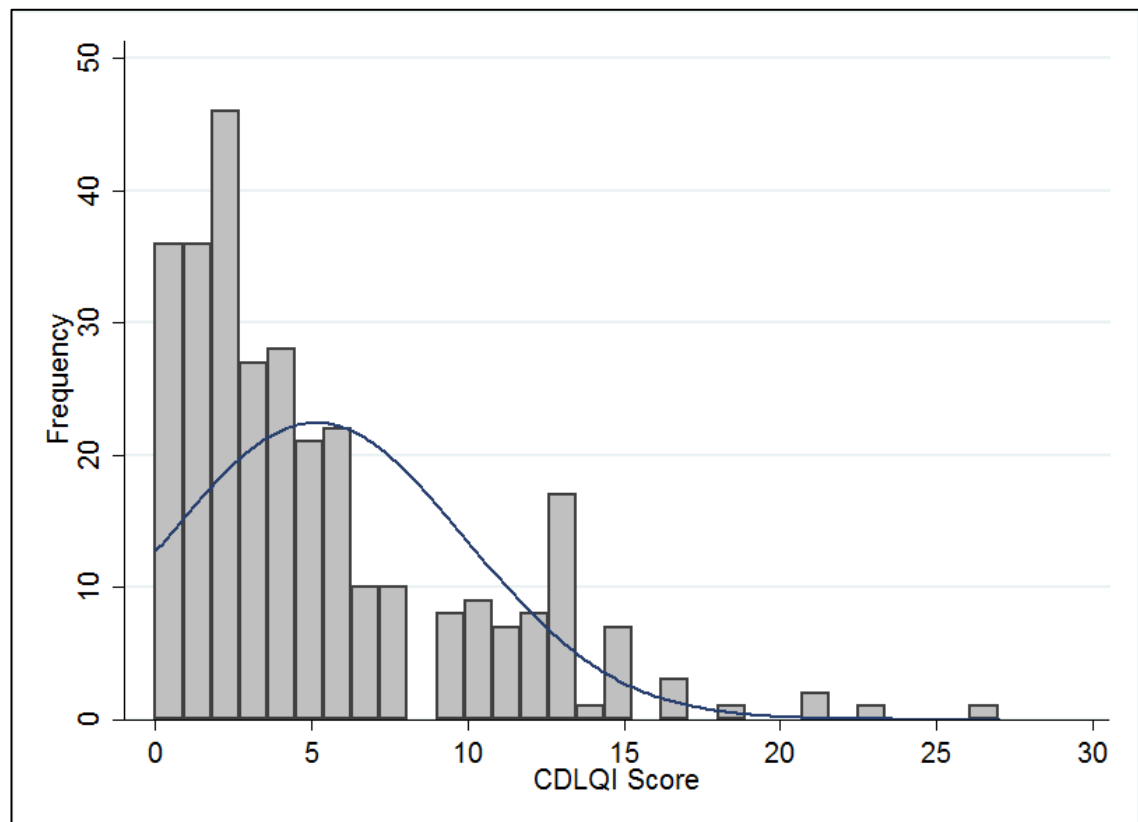
Table 42. Association between total duration of symptoms and gender, prescribed and non-prescribed medications, and number of lesions (Hazard Ratio)

	Hazard Ratio	95% CI	p
Gender	1.06	0.84 to 1.35	0.617
Prescribed medications (reported)	1.29	0.94 to 1.77	0.112
Self-treatment (reported)	1.13	0.88 to 1.44	0.344
Affected family member	1.22	0.93 to 1.60	0.141
Number of lesions ('21+' at baseline)	0.95	0.58 to 1.56	0.843

7.11 Quality of Life

Five participants returned incomplete CDLQI forms (containing no data in any fields) and therefore 301 were included within the final analysis. The distribution of CDLQI scores was positively skewed with a median (Q_1 , Q_3) of 4 (2, 7) (Figure 31), and mean (SD) of 5.1 (4.8).

Figure 31. Distribution of CDLQI scores



There was no association between QoL and duration of symptoms (measured when completing CDLQI) or presence of AE. However, female gender, greater duration of lesions at baseline, and number of lesions were all positively associated with higher CDLQI scores (greater QoL impairment) at baseline (Table 43).

Table 43. CDLQI scores at recruitment

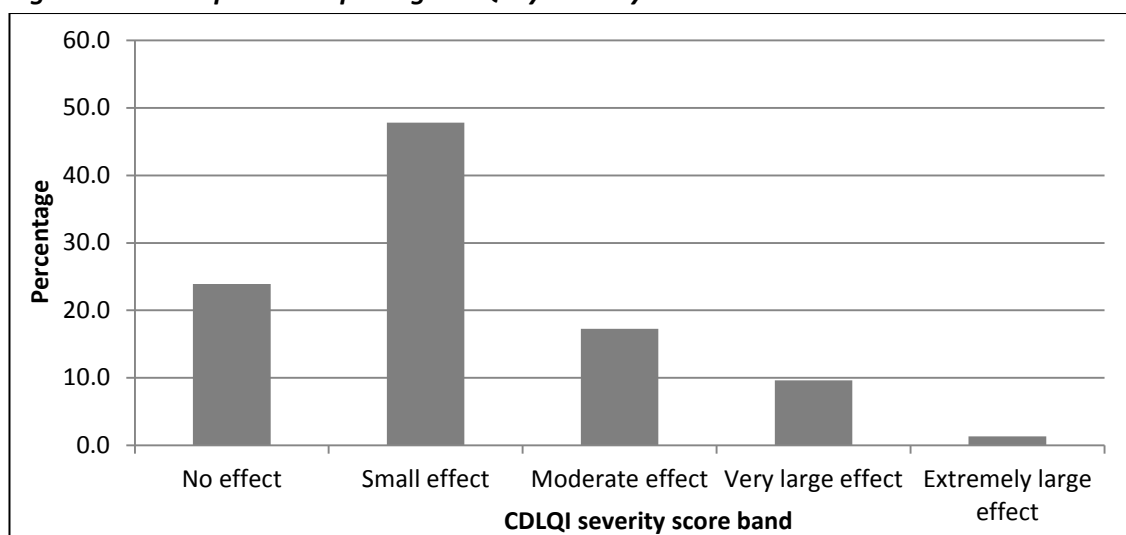
<i>CDLQI Scores</i>			
Mean (SD)	5.1 (4.8)		
Median (Q ₁ to Q ₃)	4 (2 to 7)		Max=0, Min=27
<i>By gender</i>	<i>N</i>	<i>Median</i>	<i>Q₁ to Q₃</i>
Male	137	3	1 to 6
Female	164	4	2 to 9
H=12.8, p<0.005			
<i>Referral method</i>	<i>N</i>	<i>Median</i>	<i>Q₁ to Q₃</i>
Clinical referral	29	4	2 to 8
Web referral using MCDTP	272	4	1.2 to 7
H=0.34, p=0.560			
<i>By presence of eczema (at baseline)</i>	<i>N</i>	<i>Median</i>	<i>Q₁ to Q₃</i>
Eczema present	84	4	2 to 8.5
No previous eczema diagnosis	217	4	2 to 7
H=0.76, p=0.378			
<i>By number of lesions (at baseline)</i>	<i>N</i>	<i>Median</i>	<i>Q₁ to Q₃</i>
1	20	2.5	0 to 5
2 to 5	55	2	1 to 5
6 to 10	56	2	1 to 5
11 to 15	46	4	2 to 7
16 to 20	49	3	2 to 7
21+	75	7	4 to 13
H=55.8, p<0.005			
<i>By duration lesions present (at baseline)</i>	<i>N</i>	<i>Median</i>	<i>Q₁ to Q₃</i>
<1 month	47	2	2 to 5
1-2 months	-		
3-4 months	48	4	2 to 7
5-6 months	41	4	1 to 8
6-12 month	74	4	2 to 8
>12 months	91	4	1 to 9
H=4.65, p 0.326			
MANOVA: F(57.0, 243) = 2.14, p < 0.005			
Note: ‘-’ no children in this group			

Table 44. Interpretation of CDLQI score by severity banding (70)

Score	QOL Effect
0 to 1	No effect
2 to 6	Small effect
7 to 12	Moderate effect
13 to 18	Very large effect
19 to 30	Extremely large effect

Using severity bands presented in Table 44 it indicates a small impact on QoL for most patients (70). However, 85 (28.2%) participants reported at least a moderate effect on QoL (CDLQI score >7) and 33 (10.3%) participants reported experiencing a large impact on QoL (CDLQI score >13) from their MC (Figure 32).

Figure 32. Participants completing CDLQI by severity score band



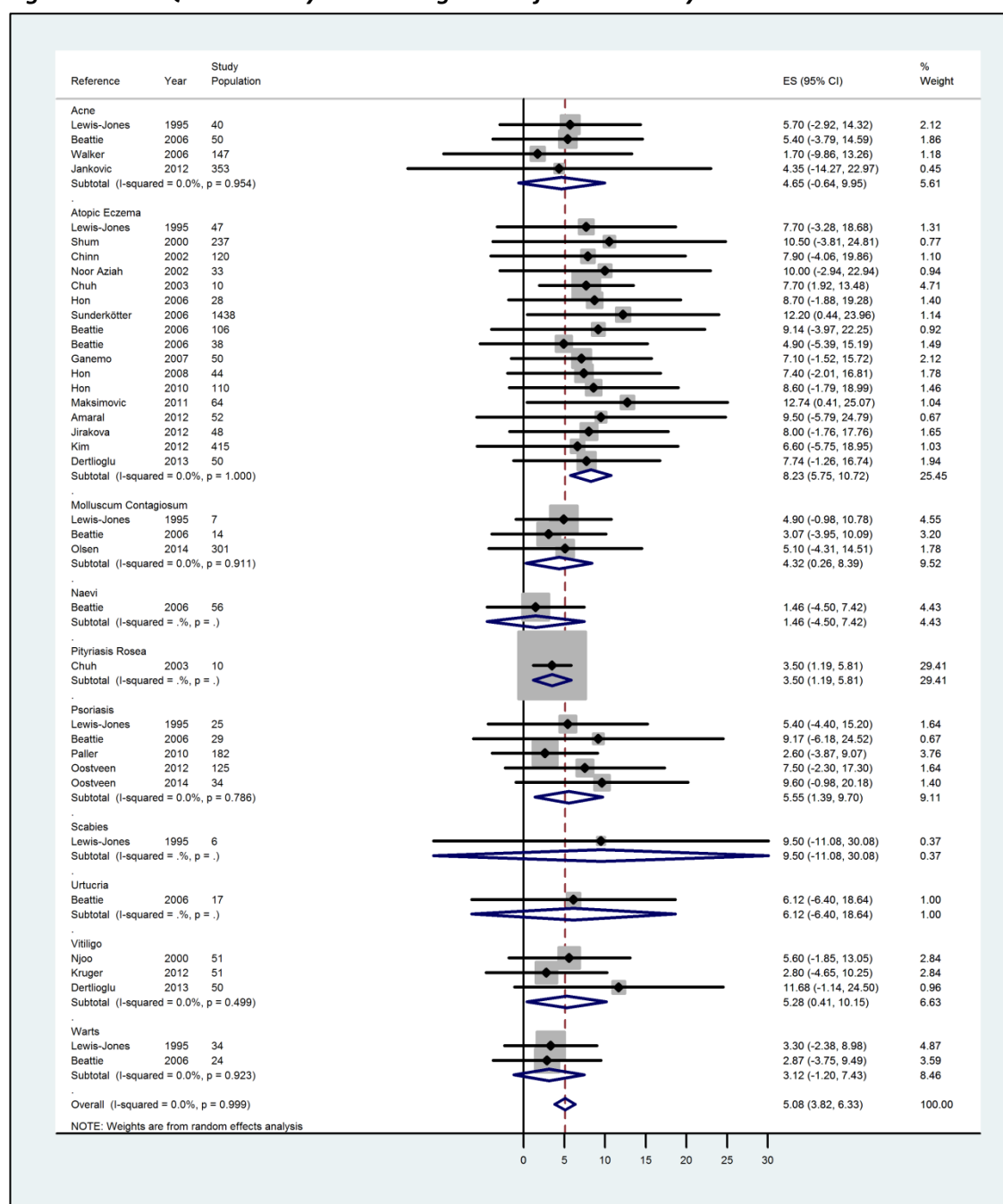
Where CDLQI scores are described by individual domains of the questionnaire the area with the highest effect on QoL is upon 'symptoms and feelings' where the impact ratio is almost double that of the other domains (Table 45).

Table 45. CDLQI score by domain

Domain	Mean (SD)	Median	Q ₁ to Q ₃	Possible total	Impact ratio
Symptoms and Feelings	2.16 (1.61)	2	1 to 3	6	0.36
Leisure	1.23 (1.86)	0	0 to 2	9	0.14
School or holidays	0.36 (0.63)	0	0 to 1	3	0.12
Personal relationships	0.49 (1.04)	0	0 to 1	6	0.08
Sleep	0.38 (0.66)	0	0 to 1	3	0.13
Treatment	0.51 (0.81)	0	0 to 1	3	0.17

The CDLQI results calculated within this chapter have been added to the CDLQI meta-analysis produced in the earlier systematic review (chapter three) in Figure 33. There is a very small change in the overall CDLQI effect from MC (mean CDLQI 4.32 from 4.15), and there is also a very small change overall in the effect of QoL from common skin conditions.

Figure 33. CDLQI meta-analysis including results from this study



7.12 Discussion

This study of 306 UK children is the largest cohort of children with MC recruited in the UK, and also the only study to prospectively follow-up children for the duration of symptoms. Children were recruited through two main routes, a clinical referral in primary or secondary care (9.5%), or self-referral by completing the MCDTP (90.5%) to confirm a MC diagnosis. Parents became

aware of the study through media advertisements, the most successful means of advertising the study were through online health forms (60%), and search engine advertisements (22.4%).

Of those recruited, 269 (87.9%) completed the follow-up within the study period, 16 (5.2%) did not respond to follow-up in two consecutive months, and 21 (6.9%) were still reporting symptoms at the study end. Children who did not complete follow-up were included within the analysis and censored at their end of study date. The time to resolution of MC in children ranged between one to 62 months, and children experienced an overall median duration of 12 months. Survival estimates show that 58% of children were clear of lesions by 12 months, 70% by 18 months and 87% by 24 months.

Transmission of MC between family members was reported in 41% of cases where parents noted that there were further cases of MC in siblings; this analysis was limited to only those living with other children aged 14 and under.

MC most commonly presented on legs, torso and arms, in 69.9% of cases lesions were present in more than one site. Over half of children had 10 or more lesions, and in a quarter of cases there were 21 or more. Less than a quarter of children had recently participated in sports (24.8%). Most children (81.1%) had their diagnosis of MC confirmed by a GP regardless of method of recruitment to the study. 60% of parents were reportedly told that the lesions would last between 12 to 18 months by GPs; this may have led to concern in 30% of cases where lesions lasted longer than this period.

To describe the impact of MC on QoL participants completed the CDLQI; 301 children returned completed questionnaires. In most cases of MC there was a small (48%) or no (29%) effect on QoL. In 10% of cases there was a very large effect on QoL, and an extremely large effect was seen in 1%. A longer duration of lesions and larger number of lesions at baseline were both associated with greater impairment in QoL, which increased when there were more than 21

lesions present. Within the six domains of the CDLQI, MC has a greatest effect upon symptoms and feelings, the mean score of this domain was double that of all other domains.

The following chapter will provide a comparison of the results presented in this chapter to other studies in the published literature (chapter eight).

7.13 Limitations

7.13.1 Potential limitations from the source of recruitment

This prospective cohort study of MC cases recruited participants through a number of different methods such as health forums and online search engines, as well as clinical referrals from primary and secondary care centres. Although recruiting through various novel methods such as health forums and online search engines generated a relatively large number of participants, there are both strengths and potential limitations to these methods that will be described here.

Limitations were that only a small proportion of participants (9.6%) were referred to the study following a clinical diagnosis by a GP or Dermatologist. Although the MCDTP provides good accuracy in parental diagnosis of MC, with high sensitivity and specificity, there is the possibility that children without MC might have completed the study questionnaires. In order to explore any effect of referral method the analyses were stratified by self or clinical referral. There were differences in the time to resolution of lesions between those who were self-referred to the study (8.9 months) and those referred by a clinician (13.3 months), suggesting that the sample referred by clinicians may represent more severe cases. However there was little difference in CDLQI scores between those recruited by the two approaches.

Recruiting through online health forums may also have introduced a bias as parents of children who are experiencing a more severe episodes of MC may be more likely to be actively searching for information about their child's condition (163). However, if anything, children

recruited by these methods seem to have less severe disease than those recruited by a clinician. In contrast by recruiting actively from the community the study limits the effect of healthcare access bias which may have occurred if only children originating from the health care setting were recruited, which may have limited the generalisability of the findings to a healthcare seeking population. By recruiting from both the community setting and primary/secondary care centres the results are more representative of cases of MC in the UK population. Both of these approaches suffer the criticism that less severe cases of MC are less likely to be detected and suggest that the prevalence estimates reported here are conservative but perhaps the impact on QoL might be an over-estimate if only the more severe cases joined the study.

It is important to recognise the benefits of using such an approach for recruitment. By allowing parents to self-refer and make the diagnosis using the MCDTP it enabled recruitment of children from over a large geographical area, and with a wide range in severity of MC. Although it might have been more secure to confirm the diagnosis by a GP or dermatologist, requiring this would invariably have led to some parents opting to not to take part and therefore resulted in selection bias. Therefore it is likely that this approach resulted in results which are more representative of the general population of children with MC.

The majority of cases were recruited by self-diagnosis, and if the study was not limited through recruitment time and had a larger number of primary care centres recruiting children, a more even split between clinical and self-referral may have allowed further exploration of the differences between groups and potential bias.

7.13.2 Potential limitations of study participants

Parents who completed study questionnaires on behalf of their children were volunteers whose participation following being informed of the study through various awareness campaigns. Participant characteristic in terms of disease presentation and socio-demographics

may differ to the population who did not participate in the research; this is a common problem in research (164). There are methods of capturing the data for all of those presenting with a disease that won't be affected by non-participation such as conducting retrospective reviews of case notes or examining routinely collected data from primary care, both study designs were considered earlier for this study. Both of these methods are also limited by the data collected in the systems, and additional questions or follow-up information cannot be collected easily. This method of data collection is also subject to healthcare access bias which limits participants to only those in the healthcare setting. It is difficult to measure the effect of selection bias, however in the discussion chapter of this thesis (chapter eight) I will discuss these results in context to those that have used inclusive data collection methods such as a case note reviews.

7.13.3 Potential limitations in data collection

Parents were asked to retrospectively ascertain when their child's symptoms had developed, advice received if MC was diagnosed by a GP, treatments that were self-prescribed or prescribed by doctors, and the presence of other skin conditions in the 12 months prior to MC development. Parents providing this information may be subject to both recall and differential recall bias when being asked to describe events that occurred in the past. Accuracy in recall can be affected by the degree of detail in questions, the significance of the events being described, significance to respondents and the time period between event and recall (165). To minimise the impact of recall bias, minimal detail was focused upon retrospective data collection and the MC questionnaires were largely based on collecting current and follow-up data, the CDLQI questionnaire captured data of the child's current symptoms.

The CDLQI provides instructions that it should be completed by a child with the help of parents if necessary. Therefore, responses may have been influenced by parental perception in

younger children. However, although all measures of QoL in younger children are likely to be imperfect, the CDLQI is a well used instrument.

7.13.3.1 *Potential limitations in measuring QoL*

The CDLQI is designed to measure dermatology specific QoL regardless of other non-skin conditions that may impact on QoL. It allows for comparisons between patients with a wide range of skin conditions (67). However, it is unlikely to be as sensitive, responsive and relevant to individual patients as disease specific instruments (112). To address this, the analysis provided QoL data according to severity of their condition, age, and natural history. These factors help to place in context the QoL effect from MC and therefore provide a detailed description, which is more sensitive to individual patients with varying severity of MC.

Participants could complete the CDLQI both on both paper and electronically via the study website. The CDLQI has not been assessed to show the extent to which it is valid for use online; however there were no significant difference in the CDLQI scores between the two data capturing methods, suggesting that the method of collection did not influence the overall results.

7.14 Conclusions

These data provide the most reliable estimates of the expected time to resolution to date, and can be used to help set realistic expectations. For most children, MC has a small effect on QoL, however, 1 in 10 children experience a very severe effect on QoL. MC appears to be highly contagious, with nearly half of the households that included additional children experiencing transmission to one or more children. These findings can be used to help inform parents and other interested stakeholders and will be discussed in the context of other published literature in the subsequent chapter.

Chapter eight: Discussion

8. Overview

This chapter will describe the main findings from the body of work presented in this thesis, consider potential limitations of these, place the findings in the context of other work in this field, consider the implications of the findings, and make recommendations for future research.

8.1 Main findings

The work presented in this thesis includes the first cohort study of UK children with MC that prospectively followed up participants for the duration of their symptoms. I developed a parental MC diagnostic tool which is the first, that I am aware of, that has been assessed to describe the extent to which it is valid in diagnosing MC in primary care and used for recruitment in epidemiological research. Finally, an update of primary care consultation rates for MC has been provided and a matched case-cohort study of children diagnosed with AE to test the hypothesis that a history of AE increases the likelihood of consulting for MC in childhood. The main findings of this work are;

- In a UK cohort of 306 children with MC aged four to 15 years, the median time to resolution of lesions was 12 months. There was variation in the time to resolution where 30% and almost 15% of children still had lesions present at 18 and 24 months respectively.
- For the majority of patients, MC has a small effect on QoL when measured using the CDLQI. Strikingly however, 10.9% of affected children within the cohort experienced a very severe effect on QoL from their MC. Female gender, greater duration of lesions at baseline, and number of lesions were all positively associated with higher CDLQI scores

(greater QoL impairment) at baseline. There was no association between QoL and presence of AE.

- Transmission of MC was common in children living in the same household. In children who lived within a household with others aged 14 years, transmission occurred in 41% of cases.
- I developed a tool which allowed parents, when aided with pictures and text, to assess whether their child's skin lesions was MC or not. The validity of the tool (MCDTP) was assessed in general practices in South Wales and provided good accuracy in parental diagnosis of MC when compared to GP's (sensitivity 91.5%, specificity 88.2%).
- We found that children aged two to seven years (12.3 to 17.8 per 1,000) consulted more than other age groups during the 10 year period 2004 to 2013. The rate of consultations declined during this period by 50.0% for both males and females.
- We found children were more likely to have a future MC consultation if they had previously consulted to their GP with AE (OR 1.13 (95% CI 1.10 to 1.16) $P < 0.005$). This was found in a matched case-cohort study of children who were diagnosed with AE by their GP compared to a control group of children with no history of an AE diagnoses.

8.2 Strengths and weaknesses of key findings

The limitations of each of the individual studies presented in this thesis were discussed at the end of the subsequent chapter. In the following section I will aim to bring together the key biases, limitations and strengths of the individual studies to discuss the importance of them being considered when interpreting the main findings of this thesis.

8.2.1 Prospective cohort study of children with MC

In chapter seven I conducted a prospective cohort study of children with MC to describe the presentation of symptoms, management (both clinical and non-clinical), time to resolution of symptoms, transmission and impact on QoL. Children could join the study by clinical or self-

referral and by recruiting through these two arms it allowed a large number of children with MC to be recruited into the study. The most successful approach for recruitment was through self-referral using the MCDTP (91% of total recruitment). Recruiting the sample by self-referral meant that children living in the community were included in the study and the results were more representative of cases of MC in the UK, it also reduced the potential bias of these findings being limited to a healthcare seeking population. However there are limitations to this approach, as only 9% of participants joined the study following a clinical diagnosis by a GP or dermatologists there is the potential that children without MC may have completed the study questionnaires. The number of false positives should be limited by the thorough development process of the MCDTP, and it is important to note that no diagnostic tool is perfect (even expert clinical diagnosis (166)) and the MCDTP has sufficiently good characteristics to warrant use in this study. Furthermore, by using the MCDTP it allowed us to recruit children from the general population, and therefore limit selection bias. When the main study outcomes were analysed between the two recruitment arms there were differences in the overall time to resolution of lesions but there were no differences in QoL (CDLQI score).

The majority of children in the study were those whose parents were seeking healthcare information about MC either through online searchers, on health forums or during a clinical consultation, and there is the potential that the results represent more severe cases of MC. Therefore slight caution should be given when generalising the findings to all cases of MC in the UK. However, as the results of this study will be provided to parents of children who are presenting with the condition in primary or secondary care by clinicians, or those seeking healthcare information from other sources such as online health websites, then these findings will be most appropriate to this population.

A strength of this study was that for the main outcomes, time to resolution of lesions and transmission of MC between children living in the same household as an index case, this data

was collected prospectively which provides greater accuracy of the data collected. Other data such as presenting symptoms and QoL were collected upon completion of the main study questionnaire which collected information of current symptoms. However, the duration of symptoms (when completing questionnaire) and management were collected retrospectively. Retrospective data collection is subject to recall bias and by limiting the amount of data collected retrospectively in this study it should limit the impact of this in the main study findings.

The MCDTP was used as a recruitment tool for those who self-referred to the prospective cohort study described here, and the next section will discuss the main strengths and weaknesses of the development and assessment of the extent to which the tool is valid.

8.2.2 MCDTP

The MCDTP was developed using a framework that was based upon forming a good disease definition for an epidemiological study that was recommended by epidemiologists (described in chapter five). The MCDTP was then assessed to measure the extent to which the instrument was valid in GP practices where a parental diagnosis was compared to that of a GP (chapter six). Although a transparent development and validation process was used for the MCDTP there are some key limitations in these methods that will be discussed here.

The gold standard MC diagnosis was provided by GPs and although they will diagnose the majority of MC cases in the UK, with only a small proportion of children being referred to dermatologists, it may suffer the criticism that dermatologists are the true gold standard for diagnosing skin conditions in the UK. To measure agreement between the gold standard diagnosis used in this study with three clinical experts (two consultant dermatologists and a second GP with expertise in dermatology) the diagnosis provided high levels of agreement suggesting that the GP diagnosis is likely to be reliable.

The images used in the MCDTP were of lesions on white skin colour and although the clinical description of MC remains the same, this may limit the acceptability of the MCDTP to a more diverse population. Where the characteristics of the practice populations which participated in measuring the extent to which the MCDTP is valid are examined they provide similar data to that of England and Wales, suggesting that the MCDTP is acceptable for use in this population. No data of ethnicity was collected from participants completing the MCDTP and this is a limitation, if this data were collected we would have been able to describe the test characteristics between populations based on ethnicity.

The development of this tool involved a comprehensive process that involved multiple key stakeholders. In particular, we sought to ensure that the language used in the tool was understandable to a lay audience, as even the most commonly used medical terminology should be carefully explained to parents to avoid confusion (129).

Chapter four described consultation rates for MC in a retrospective longitudinal study of MC cases and a case-cohort study of AE, the next section will discuss the main strengths and weaknesses of this study.

8.2.3 Primary care consultation for MC

Within chapter four data was extracted from the CPRD database to describe the incidence of primary care consultations for MC in the UK and associations with AE. The CPRD database is the largest database of primary care consultation data in the UK and represents almost five million patients. Extracting routinely collected data of primary care consultations from large retrospective databases is useful for identifying the burden of a specific condition within the primary care setting and trends of consulting during a specified time period but this study design is subject to limitations which will be discussed here.

The data held within CPRD are not inclusive of all UK general practices, however, data are validated and found to be generalizable to the UK population, and the statistical analysis used in the study provides the range in which we believe the true estimates of MC consultations in the UK will lie. The analysis performed in this study is limited by the assumption that the data extracted is correct, therefore the numerator within the analysis will not under or over report incidence of MC. By the data being extracted by an experienced research analyst this should limit errors in the extraction process.

As MC is a self-limiting condition and the most common management by GPs in the UK is for the condition to be left to resolve naturally, in these instances where clinicians are providing only verbal advice without treatments a Read-code for MC may not be recorded in the system or the diagnosis could be described as 'free text'. This is a limitation of routinely collected datasets and our findings where no 'free text' data were extracted or analysed in this study, therefore the consultation rates provided may under-report the true number of MC diagnoses in primary care. When describing the relationship between AE and MC it must be noted that this is a conservative calculation of risk as it includes only those with a confirmed diagnosis of either MC or AE entered as a Read-code, the true prevalence of both conditions in the community may indeed be higher.

For the retrospective longitudinal analysis, we were unable to assess the different ways MC is managed by GPs, although data of the management of MC in primary care was collected and discussed in chapter seven. There are also limitations in the assumption of correct recording of data held within CPRD; the database relies upon accurate recording of consultations by the GP, however by only including "up to standard" data the impact of this source of error will likely be reduced.

The next section will describe the findings presented in this thesis and interpret them in the context of other published work.

8.3 Interpretation of findings and comparison with other published work

8.3.1 *Time to resolution*

Results of the systematic review in chapter two highlighted that the time to resolution of lesions is poorly described in the literature. The best available data was based upon two small studies in the 1960's (Alaska:n=13, Fiji:n=14) which described the time to resolution as between two weeks and 24 months (13), and a mean duration of eight months (47). The data presented in this thesis, of a much larger prospective cohort of children, suggests an average time to resolution as 13 months. Variation in time to resolution is large, with approximately 60% of children having all lesions resolve by 12 months, 70% by 18 months, and 90% by 24 months. Combining this data with our finding that 60% of parents are being told that the lesions will last between 12 and 18 months suggests that many parents are not being given accurate information about the true prognosis of the condition.

8.3.2 *Transmission of MC within households*

A high proportion of children described further cases of MC in siblings aged 14 and under living within the same household (41%). Data can be compared to data collected in Alaska where 10 children were followed up for the duration of their condition and two new cases of MC were reported in family members (13), this figure is lower from the data within this thesis however in Alaska it was not reported whether all 10 children did indeed cohabit with other children and this study included only a very small sample of data collected during the 1960's.

8.3.3 *Quality of Life*

A key finding of this research was that around 10% of children experience a large or very large impact on QoL. Tests of association showed a higher CDLQI score in those presenting with a higher number of lesions which typically would be a contributing factor in QoL impairment. Although other studies have used the CDLQI in children with MC, I am not aware of any that

have provided a detailed distribution of CDLQI scores and associations with the presentation of the condition.

The mean CDLQI score was slightly higher than those previously reported (3.1 (73), 4.9 (67)) but were within the same severity banding. Both previous studies and the findings within this thesis provide a mean CDLQI score that describes the condition as having a small effect on QoL. Where CDLQI results are combined within a meta-analysis of common skin conditions there are marginal differences in the overall effect from MC once the results of this thesis are included, suggesting these results are within the range of other published data. A study which examined QoL of MC using a short un-validated questionnaire showed that parents were significantly more concerned about MC than their child, with 82% of parents (n=23) stating 'it concerned them moderately or greatly', compared to 43% of children (23). This suggests that our data may have underestimated the effect on QoL for younger children where 30% reported at least a moderate effect on QoL. Although our study did not examine QoL upon family members, instruments designed specifically for the purposes of describing the impacts upon family members highlight that family members may experience psychological distress as much as, or in some cases more than, the patient (167).

8.3.4 Primary care consultations for MC

Two studies were identified in the initial systematic review (chapter two) which described primary care consultations in the UK for MC (5, 26). Both studies showed that the greatest consultation rate was in children aged one to four years (15.0 to 17.2 per 1,000), neither of these studies presented data separately for children aged zero to 14 years in individual age bands, instead presenting these as a five to 14 age group. By un-grouping children aged one to 14 years our data highlights that MC consultations are greatest in those aged two to seven years (12.3 to 17.8 per 1,000). The behaviours of these groups, which may reduce the

opportunities for skin to skin transmission, could explain why there are differences in incidence rates.

Modelling the consultation rates of MC calculated in this thesis with the most recent general practice population published for England and Wales by ONS for 2011 (108), and assuming a similar practice structure by age band for a hypothetical practice population of 6,000, provides an estimate that an average practice would experience 11 recorded consultations for MC per year in children aged one to 14 years. This figure is less than that previously published in 2005 that estimated a practice with a population of 10,000 would expect to see 24 new cases of MC per year: 90% of those being children ($n=21.6$) (5). However this figure included adults, and when adults are removed and this figure is crudely calculated for a practice size of 6,000 it estimates 13 cases of MC per practice which is consistent with our data.

8.3.4.1 Seasonality

Data collected from Dutch general practices in 1987-88 described the seasonality of MC consultations and showed peaks during the months January to March and April to June (43). These findings are similar to the data presented in within this thesis where the rates were highest in the same two quarters and peaked during the months April to June. Without an understanding of the route and opportunities for transmission, little explanation for this seasonality in incidence rates can be given. Some possible reasons could be more outdoor activity during this period, increased skin trauma (from physical activities), children wearing less clothing, more insect bites and that early in the calendar year is when primary schools provide swimming lessons; and as swimming is shown to increase the risk of transmission this could cause an increase in consultations. Skin and soft tissue cell infections have a higher rate of consultations during the summer months (168) and the peak of MC consultations during June in our results suggest a similar pattern.

8.3.4.2 Trends in consulting for MC

Annual trends of MC consultations to primary care in the UK were previously reported for the period 1994 to 2003 (5), where the incidence rate rose by 38.5% (8 to 13 per 1,000) from 1994 to 1998. The rates remained constant until 2002 until there was a decrease in the rate during 2003. Our analysis of data extracted from CPRD since 2004 continued this decline continuously for the full 10 year period of study data. The decrease in primary care consultations for MC may be caused by the increased availability of health care information online (169) which has seen a reduction in parents presenting to primary care where adequate information is available on health websites for parents to manage a condition at home (170). Caution must be given when obtaining healthcare information online as this is generally not monitored.

A second consideration for the decreasing trends in consultations for MC may be due to the decreasing trends in some infectious diseases within Western populations, such as the UK. Reasons for reductions in some infectious diseases during the past century may be due to improved sanitary conditions, less extreme poverty and a decrease in large numbers of children living within one household. For MC, limited close contact to other children with the condition and improved sanitary conditions could significantly reduce the opportunity for transmission between children and the overall prevalence of the condition within the population.

8.3.5 Relationship between MC and AE

AE has been shown to be associated with abnormalities in immune regulation, and patients with AE are known to be more susceptible to a range of cutaneous infections (8). The results of the prospective cohort of children with MC highlighted that 34.6% of parents completing the survey described a second dermatological condition in the months prior to MC. The most common condition was AE (28%), a wide range in the prevalence of AE in children presenting with MC has previously been described as 18.2% (48), 24% (3), 30% (45) and 43% (52). These

studies did have a different study design to our prospective community cohort, where all three retrospectively reviewed the case notes of children who had been diagnosed with MC at dermatology secondary care centres. None of the children were recruited in the UK but in Greece, North America, and France. We can assume that there is a high prevalence of AE in children who are diagnosed with MC and estimate that between 18% to 40% of children will develop AE. Comparing this figure to the general population, in Greece a national survey described the prevalence of AE in children as 5% (48), although in the UK a national survey described a lifetime prevalence of AE in children aged 12 to 14 as 22.5% (171), and the presence of AE in the previous year as 12% in children aged two to 11 years (172). The lifetime prevalence of AE reported in the general population is slightly lower than that in children with MC, and an AE diagnosis within the previous 12 months is less than half that of children with MC suggesting that the prevalence of AE is higher for children with a current MC diagnosis compared to those without.

A prospective observational study in a paediatric outpatient clinic in Brazil found no relationship between MC and the presence of AE (56), this was comparing children who presented with MC, AE, and both MC and AE, and included no comparison to a control group. North American children diagnosed with MC aged five years and under were more likely to have a current AE diagnosis (OR 2.51 (95% CI 1.10 to 6.01) $p=0.029$) or to have either a current or previous AE diagnosis (OR 3.58 (95% CI 1.77 to 7.55) $p<0.05$) than controls when examining routinely collected data extracted from the Indian Health Service. The matched cohort study of AE cases in this thesis tested the hypothesis that children who have a history of AE are more likely to have a future MC consultation during childhood and is the first, that I am aware of, that retrospectively examined both a group of AE cases and control group. The results showed children were more likely to have a future MC consultation during childhood if they had previously consulted with AE than controls (OR 1.13 (95% CI 1.10 to 1.16) $P<0.005$).

In summary, the presence of MC is often accompanied by AE, and the prevalence of AE in children with MC is higher than that in the general population. Where a cohort of children with AE were compared to age sex matched controls it shows that children who have a history of AE are more likely to have a future MC consultation during childhood than controls. The risks associated with the development of MC, and factors increasing the opportunities for transmission of MC in children remain unclear and further research is required into this area.

8.4 Lay representation

There is little reflection of the overall experience of involving lay representatives in the research process and of the nature and level of involvement within the published literature (173). Here I aim to provide some insight of the experiences of lay representation for this research.

SW joined the research team as a lay representative and contributed significantly to the design phase of the development and assessing the extent to which the MCDTP is valid by proof reading patient information leaflets and by providing overall feedback and direction in the processes and procedures involved in recruiting participants in GP surgeries. The feedback SW provided in ensuring that clear understandable language was used in the MCDTP and the suggestion of a study envelope in the validation of the MCDTP, which avoided receptionists asking potentially sensitive questions, proved effective in the recruitment of parents across most practices.

Overall SW attended three meetings at Cardiff University, and discussed patient information documents or procedures via email on several occasions. During the end of 2013 communication reduced significantly and after two months I received an email explaining that due to family circumstances (bereavement) and a new job she would be unable to continue to support the project. Having a lay representative involved in the project was rewarding and useful to the final study design but as a volunteer there must be limited expectations of

commitment which can be provided. There is the potential for other life commitments to contribute to a lay representative's ongoing involvement in the study which was experience here. Evidence has suggested that lay representative can also provide insight to the data analysis and interpretation phases of research (33), and in the case of this research, insight did not extend this far. In summary, the involvement of SW enhanced the study design and procedures of the research positively; potential difficulties that may have arisen during recruitment in GP surgeries were avoided by the input of a lay representative. From this experience I would advocate the importance of having a lay representative involved in research projects but also provide caution to the expectations of their on-going involvement.

8.5 Implications and further research

8.5.1 Advice for parents and clinicians

Key information a parent may wish to know about their child's condition are; the causes of illness, implications of the condition, and future prevention (174). This information can be gained from epidemiological research such as the data collected from this study. By providing this information it can improve the experience during a consultation for both parents and clinicians. Our findings suggests that potentially GPs have been providing incorrect advice when describing the prognosis of MC to parents and this is mainly due to a lack of epidemiological data regarding MC, which was highlighted in chapter two. 60% of parents were told by GPs that their child's lesions would last between 12 to 18 months and this may lead to concern in 30% of cases where the time to resolution of lesions may be longer than this period. This finding alone highlights the importance of distributing the findings from this thesis to ensure advice clinicians are providing uses the most recent evidence that this thesis can provide. The findings from this thesis suggest that the advice GPs should be giving to parents following an MC diagnosis in their child is;

- MC is a common condition in children, most common for those aged one to nine years.

- The average time to resolution of lesions is 13 months; however for 30% of children they will still be present at 18 months and 10% at 24 months.
- Transmission between siblings is high and can occur in 40% of children who have other children living within the same household.
- Although the time to resolution of lesions can be significant, generally it should have no or a small effect on QoL.
- There is little evidence of the causes of transmission or behaviours that will reduce the risks of transmission between family members.

8.5.2 Dissemination of findings

The two main methods used to disseminate the findings from the studies in this thesis were in scientific peer-reviewed journals and via a study specific website. The website was made freely available to both parents and clinicians (website address: www.molluscum-info.com). It is also important that these findings are provided elsewhere in sources such as information leaflets or health information websites online as by providing information about conditions in these sources it can have the potential to reduce consultations for minor conditions if parents have access to this information at home (175). This approach could be adopted for MC where parents could both diagnose and manage the condition at home without requiring a clinical consultation to confirm a diagnosis. The website hosting the MCDTP and URL went live in March 2014 and in the subsequent eight months it had 984 visits from 868 unique users and 2,568 page views. A link to the website was included in a news article about MC published in the Daily Mail Online on the 7th October 2014 (176), in this article readers wishing to read more information about MC or view the MCDTP were directed to the study website. The website can also be promoted in primary care where GP practices can include a link from their practice website.

8.5.3 Challenging clinical perception of MC

MC is often thought as being a trivial self-limiting condition by clinicians (2). However, most children will have lesions lasting more than a year, and one in 10 children will experience a very large effect on QoL. A higher effect on QoL is more apparent in children who have a greater number of lesions, and the greatest impact is on symptoms and feelings. Therefore, the notion that MC is always a benign, trivial illness needs to be challenged, and active treatment should be considered for some children, especially those with larger numbers of lesions and those with higher CDLQI scores.

8.5.4 Alternative management of MC in severe cases

Treatments of MC for severe cases should be considered by clinicians. The findings of this thesis would suggest that children with severe MC, having more than 21 lesions, and those with CDLQI scores greater than 12 (very or extremely large effect on QoL) should be considered for therapy. The current UK guidelines of treatment algorithms for psoriasis by the National Institute for Health and Clinical Excellence (NICE) suggest drug regimens based upon both a PASI (177) and DLQI (178) score (179). MC guideline developers should consider recommending that the CDLQI score and / or the number of lesions present should be taken into account when making management decisions, similar to NICE guidelines for psoriasis.

8.5.5 Future uses and developments of the MCDTP

The MCDTP was developed and provided good accuracy for use in children in the UK to allow parents to diagnose their child's skin lesion as MC. The sample population used when assessing the extent to which the instrument is valid suggest that it is acceptable and generalisable for use in the UK or for populations with a similar demographic. The MCDTP is available online and recent publications have encouraged healthcare practitioners and organisations to promote use of the site and provide a link on their websites (180). The site could also be used for education and training purposes, and the website and/or paper tool could be used to identify

suitable patients for inclusion in other studies on MC. Factors such as parent confidence in their diagnosis can be incorporated into future epidemiological studies or primary care screening tools if a higher accuracy was required.

The MCDTP could potentially be used in other more diverse populations but it would require further development of the language if translated and images used, potentially using children of varying skin colours. If a different version of the MCDTP was created I would suggested that a similar development and validation process to that used in this thesis.

8.5.6 Recommendations for future work

8.5.6.1 Improving knowledge of basic science of MC

Epidemiological studies of MC have highlighted risks that are associated with a higher prevalence of MC in children, however currently there is little evidence describing the causes and routes of transmission in the development of MC in children. There is a clear gap in the basic scientific knowledge of MC to provide an understanding of the mechanisms of transmission and the causes of spontaneous clearing of the condition for healthy children; this gap in knowledge has been highlighted previously by clinical virologists (4) and this research has only further highlighted the importance of this knowledge for MC.

8.5.6.2 Treatments Trials

Recent reviews of treatments for MC have recommended the natural resolution of MC in children, and for most children this will be the most appropriate management. However for those who have a more severe episode of the condition and experiencing a significant effect on QoL (approximately one in 10 children) treatment should be considered. Parents and children may become frustrated with the significant time to resolution of lesions and may turn to alternative treatments for MC which are advertised widely on internet search engines when seeking information about MC. One treatment which has had much publicity for treating MC is *MolluDab* (5% potassium hydroxide) which is available both with and without prescription. A

treatment trial of potassium hydroxide showed that it did lead to a greater resolution of lesions compared to controls, however these differences were not statistically significant (181). Without the availability of a recommended treatment of MC further treatment trials are required to assess the effectiveness of therapeutic approaches in children with more severe MC. Any future treatment trials should be based upon the recommendations of the 2010 Cochrane review of treatments for cutaneous MC (17).

8.5.6.3 Cost analysis of MC treatments

A cost-benefit analysis should be conducted to assess the feasibility of changing current clinical guidelines regarding the treatment of MC in children. The cost-analysis of treatments to the NHS and clinical commissioning groups should be conducted alongside any future treatment trials. Data collected within this thesis could be used to model potential treatment algorithms based upon CDLQI scores, MC severity and the number of children that consult to primary care or are referred to secondary care with MC.

8.5.6.4 Describing the prevalence of MC

Further research could aim to establish the prevalence of MC in the community; this is one element of the epidemiology of MC that still remains not very well described in the scientific literature. However, the justification of a prevalence study would need to be clearly defined as this type of study design can be expensive and burdensome to researchers. It would also be important to consider that those who do not present to a clinician with MC may be successfully managing the condition at home and that their lesions may be generally asymptomatic. Therefore I would suggest there is little benefit of a prevalence study and would question whether describing the prevalence of MC would indeed benefit the research field or change current clinical management.

8.6 Conclusions

This thesis identified gaps in the current epidemiology of childhood MC and aimed to address this gap in evidence by conducting a longitudinal study of children presenting with MC in primary care and a prospective cohort study of children with MC in the UK. The research within this thesis has described the presentation of symptoms, management, time to resolution, transmission between family members, QoL, and associations between AE and MC. These findings have been made available to parents and GPs through an information website for MC, and also through publications in the scientific literature.

Consultations in primary care are greatest in children aged two to seven years, and the rate of consultations have reduced significantly by 50% since 2004 to 2013. The presence of MC is often accompanied by AE and children who have a history of AE are more likely to have a future MC consultation during childhood than controls. The risks associated with development of MC are not clear, and further research is required into this area, as with describing why there is a large variation in the time to resolution of lesions between children.

MC is often perceived by some clinicians as being a trivial self-limiting condition (2), but data suggest that for a significant minority of children this is not the case. The time to resolution of lesions on average is 13.3 months but parents should be aware that for 10% of children lesions may not have resolved by 24 months. For almost half of children parents described that there were further MC cases within the household. Children with a greater number of lesions (21 or more) are more likely to experience a greater impact on QoL. Therefore, the notion that MC is always a benign, trivial illness needs to be challenged, and active treatment should be considered for some children, especially those with larger numbers of lesions and those with higher CDLQI scores. Further studies are required to assess the effect of therapeutic approaches in children with more severe MC.

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Appendices

Appendix 1 – Published manuscripts

- 1.1 Systematic Review (Epidemiology of childhood molluscum contagiosum)
- 1.2 Development and Validation of MCDTP: diagnostic accuracy study in primary care.
- 1.3 Time to resolution and impact on quality of life of molluscum contagiosum in children: a prospective community cohort study.
- 1.4 Conference abstract (MCDTP Design)

Appendix 2 – Appendices relating to systematic review (chapter two)

- 2.1 Systematic review MESH headings

Appendix 3 – Appendices relating to MCDTP development and validation (chapters five and six)

- 3.1 Dermatologist structured interview/questionnaire
- 3.2 Topic guide
- 3.3 MCDTP pilot questionnaire for parent group
- 3.4 Molluscum contagiosum info sheet for GPs
- 3.5 Letter of invitation to join MOSAIC study sent to practice managers
- 3.6 MCDTP Validation - Participant study pack
- 3.7 Medical photography protocol

Appendix 4 – Appendices relating to prospective cohort (chapter seven)

- 4.1 Molluscum contagiosum cohort questionnaire
- 4.2 Children's dermatology life quality index (CDLQI)
- 4.3 GP practice MOSAIC study information cards
- 4.4 Western Mail printed article about molluscum contagiosum and MOSAIC study
- 4.5 Kaplan-Meier survival estimates of MC lesions

Appendix 5 – Ethical and research governance approval documentation

- 5.1 Research ethics committee (REC) approval
- 5.2 Research governance approval (Cardiff and Vale UHB)

5.3 Research study sponsorship

5.4 Independent scientific approval committee (ISAC)

5.5 CDLQI permission

5.6 WSPCR funding decision

5.7 Letter of access for research (Cardiff and Vale UHB)

Appendix 1 – Published Manuscripts

1.1 Systematic Review (Epidemiology of childhood molluscum contagiosum)

Olsen JR, Gallacher J, Piguët V, Francis NA. Epidemiology of molluscum contagiosum in children: a systematic review. *Family Practice*, 31(2). 2014 pp.130-136



Epidemiology of molluscum contagiosum in children: a systematic review

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Abstract

Background. Molluscum contagiosum (MC) is a common skin condition that primarily affects children, a common reason for presenting in primary care and is commonly seen in children presenting with other conditions in primary and secondary care. It is usually asymptomatic but can present with pain, pruritus, erythema and bacterial superinfection.

Aim. To synthesize the current epidemiology of MC.

Design and setting. A systematic literature review of bibliographical databases on the prevalence, incidence, risk factors, age distribution and association with other conditions for MC in children.

Results. Data on the epidemiology of MC is largely of poor quality. The largest incidence is in children aged between 0 and 14 years, where the incidence rate ranged from 12 to 14 episodes per 1000 children per year. Incidence rates in the UK were highest in those aged 1–4 years. Meta-analysis suggests a point prevalence in children aged 0–16 years of between 5.1% and 11.5%. There is evidence for an association between swimming and having MC and MC is more common in those with eczema; however, there is little evidence for other risk factors.

Conclusions. MC is a common condition, with the greatest incidence being in those aged 1–4 years. Swimming and eczema are associated with the presence of MC, but the causal relationships are unclear. There is a lack of data regarding the natural history of MC and published data are insufficient to determine temporal or geographic patterns in incidence, risk factors, duration of symptoms or transmission between family members.

Key words: Common illnesses, dermatology, epidemiology, pediatrics, primary care, quality of life.

Introduction

Molluscum contagiosum (MC) is a common skin condition, caused by a member of the poxvirus family (1,2), that causes considerable parental anxiety and results in primary and secondary care consultations. It is common in children and generally presents with asymptomatic lesions; however, it can present with pruritus, erythema and, on some occasions, bacterial superinfections with inflammation and pain (3,4). Dermatological conditions can impact upon quality of life; in severe cases, they

can have similar impacts to that of chronic conditions (5). The reported incidence and prevalence of MC varies widely, therefore it is difficult to estimate the true number affected by MC. Evidence of factors increasing the risk of transmission is mixed.

In children, there are few treatment options available for clearing of MC lesions. Treatments such as curettage are particularly unpleasant and often lead to pain and scarring (1,3). A Cochrane Review of treatment for cutaneous MC in 2010 recommended

MC to be left to heal naturally until better evidence for superiority of other treatment options emerge (6). Most patients who visit the doctor wish to leave the consultation with a prescription (7), thus parents may be uncomfortable without being prescribed a treatment following their child's MC diagnosis. In these instances, it is important that clinicians have accurate information available about the prognosis and management of MC.

There is a paucity of carefully synthesized data on the epidemiology of MC. Therefore, we set about to address this gap by conducting a systematic literature review on the prevalence, incidence, risk factors, natural history, age distribution and association with other conditions for MC in children.

Methods

Data sources

We conducted a systematic search of bibliographical databases using a predefined search strategy in October 2012. Articles were also identified from reviews of citations within articles, a preliminary scoping exercise using 'Google Scholar', and identification of articles by experts in the field.

Medical subject headings were used in Ovid^{SP} to search the Medline (1946 to October 2012), Embase (1947 to October 2012) and Cochrane databases. Duplicates were removed and the search was restricted to English language and studies involving humans.

Data extraction and analysis

All publications identified in the search were screened by title and abstract using the inclusion criteria below. The full texts of all articles that might have been potentially relevant were requested for full review by one author (JO) using a template covering key study characteristics, incidence and prevalence of MC, age distribution, risk factors and other conditions associated with MC.

Inclusion and exclusion criteria

Articles were included if they were original research articles on the incidence, prevalence, risk factors, age distribution or other conditions associated with MC in children. We excluded studies if they were nonoriginal research, review papers, singular case reports, treatment trials or related exclusively to adults, immunocompromised individuals, those attending sexual health clinics or dental MC. We included studies if they related to both children and adults and, where possible, extracted only the data that pertained to children.

Results

Our search identified 441 articles. After reviewing the abstracts of all 441 articles, 25 publications met our inclusion criteria (Fig. 1). Data, where available, was extracted for analysis.

Incidence of primary health-care consultations for MC

All studies on the incidence of MC used routinely collected data. We found two studies that explore the incidence of MC in England and Wales (8,9) using routinely collected data from the same sentinel practice network (Weekly Returns of the Royal College of General Practitioners), representing a population of 950 000; the first study collected data over a 10 year period (1994–2003), and the most recent over a single year (2006). Both studies found similar incidence rates, the greatest incidence being in those aged 1–4 years (15.0–17.2 per 1000; Table 1). There was little variation in incidence rates between genders.

A study of North American Indians that involved extracting routinely collected data over a 5-year period (2001–05) about patients attending outpatient departments found an annual incidence rate of 2.01 per 1000 (11). The peak incidence was in the 1- to 4-year age group (10.2 per 1000), and 5 to 14 year olds had a higher than average incidence rate (4.04 per 1000).

The largest incidence of MC was reported in Holland (25 per 1000) where data were extracted for a period of 12 months (1987–88) from 10 general practices of routinely collected data with a total study population of 332 200 (10). However, this rate was calculated for only those aged 10 years. Regional differences in incidence rates were found in different regions of Holland, ranging from 1.0 to 3.2 per 1000. The author noted no differences in the climate, temperatures or urbanization between the areas, with very similar rates reported in each population size examined. Regional differences were also found in North America (11), where differences were consistent across all 5 years of study data examined and, again, there was no explanation that could attribute a higher incidence to a region.

Population prevalence

The prevalence of MC was described in eight articles (Table 2). No article reported the prevalence of MC in Western Europe or North America. Studies reporting the prevalence in children in a variety of settings in Israel, Romania, New Guinea, Mali, Japan and Turkey described a prevalence of MC ranging from 0.27% in 6 to 12 year olds in Romania (12) to 34% in 2–9 year olds in Israel (13).

The study population that is most similar to Western Europe and North America, in terms of economic development, is Japan, where two studies in children aged 4–11 and 0–6 years showed a point prevalence of 6.9% (15) and cumulative prevalence of 19.7% (19). Both were cross-sectional studies of children where parents were asked to recall a diagnosis of MC for their child.

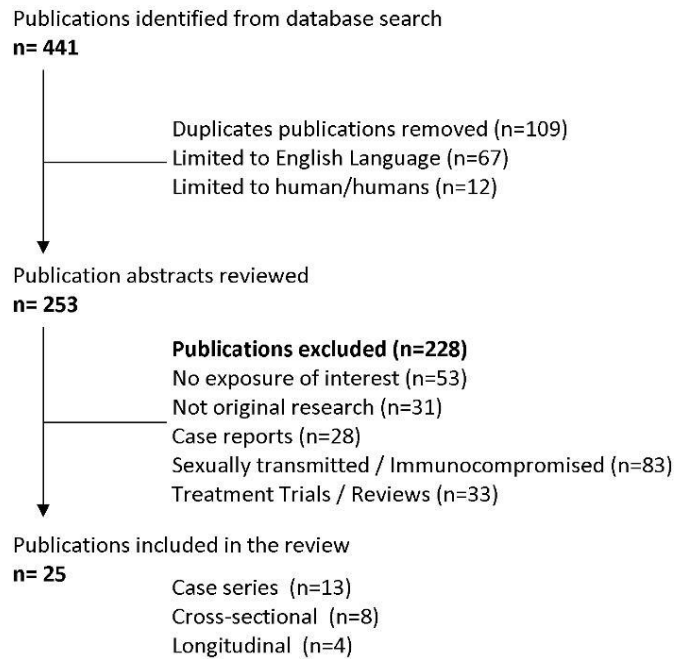


Figure 1. Flow chart of study selection process

Table 1. Incidence of MC (number of new cases of MC per 1000 study population during specified time period)

References	Data	Age group (years)	Population	Sex	Annual incidence (per 1000)	95% CI
Koning <i>et al.</i> (10)	1987–88, Holland	10	–	M&F	25.0	–
Pannell <i>et al.</i> (8)	1994–2003, UK	1–4	119 920	Male	15.0	14.4–15.8
			113 382	Female	15.2	14.5–16.0
		5–14	321 124	Male	10.7	10.4–11.1
			306 615	Female	10.5	10.1–10.8
Reynolds <i>et al.</i> (11)	2001–05, North America	1–4	–	M&F	7.7	–
		5–14	–	M&F	3.1	–
Schofield <i>et al.</i> (9)	2006, UK	1–4	–	Male	17.2	–
			–	Female	15.5	–
		5–14	–	Male	9.5	–
			–	Female	10.7	–

–, missing data; M&F, male and female.

Two studies reported a point prevalence that was considerably higher (34% and 22%) than that was found in other studies. The first of these was conducted in a small rural community in the warm and dry climatic area of the Jezreel Valley, Israel, following reports of a small epidemic in 1991 in 2–9 year olds (13).

The other was a study of those aged 0–10 years in 16 villages in the West Sepik District of New Guinea, which was identified due to a larger number of cases of MC in the village (14). The lowest point prevalence reported was 0.27% in Romanian school children aged 6–12 years (12).

Meta-analysis of prevalence data gives an overall estimated weighted prevalence in children of 8.28% (95% CI 5.1–11.5); however, when the three studies with a considerably higher rate are excluded, due to potential outbreaks and a lifetime prevalence recorded, the estimated prevalence is lower 2.83% (95% CI 0.0–5.9; Fig. 2).

Gender

There was no evidence of a difference in prevalence by gender, with the proportion of males ranging from 41.2% to 62.0% and confidence intervals including 50% in most studies (Table 3).

Risk factors

Swimming

There is an association between a recent history of swimming and development of MC in children (Table 4). The risk of MC amongst swimmers is nearly twice [relative risk (RR) 2.3 CI 1.65–3.21] that of nonswimmers (20). Similarly, the risk in frequent swimmers is about twice as high (RR 2.0 CI 1.25–3.20) as the risk in those with low-frequency swimming pool use (15).

In Brisbane, all persons diagnosed with MC from primary and secondary care centres during a 5-month period were invited to undertake a dermatological assessment and interview about swimming pool use ($n = 210$, age 0–47 years) (21). The study

Table 2. Reported prevalence of MC (number of cases identified within study sample per 100)

References	Location	Age group (years)	Population	Cases	Prevalence	95% CI
Sturt <i>et al.</i> (14)	New Guinea	0–10	78	17	21.8	12.6–31.0
Niizeka <i>et al.</i> (15)	Japan	4–11	7472	517	6.9	6.3–7.5
Oren and Wende (13)	Israel	2–9	81	28	34.6	24.2–44.9
Mahe <i>et al.</i> (16)	Mali	0–12	1817	65	3.6	2.7–4.4
Popescu <i>et al.</i> (12)	Romania	6–12	1114	3	0.3	0–0.6
Tuncel and Erbagci (17)	Turkey	14–16	166	2	1.2	–0.5 to 2.9
Tabari and Shakerian (18)	Iran	1–5	986	21	2.1	1.2–3.0
Hayashida <i>et al.</i> (19)	Japan	0–6	913	180	19.7	17.1–22.3

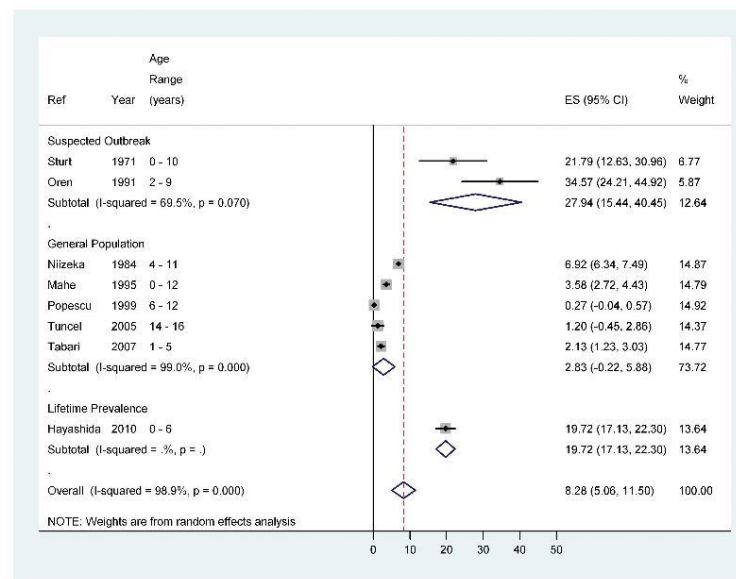


Figure 2. Comparison of prevalence of childhood molluscum contagiosum reported in cross-sectional surveys by study subset

Table 3. Gender distribution of children with MC

Gender					
References	Sample	Male	Female	Proportion males (%)	95% CI
Sturt <i>et al.</i> (14)	401	217	184	54.1	49.2–58.9
Oren and Wende (13)	34	14	20	41.2	26.4–57.8
Castilla <i>et al.</i> (20)	24	16	8	66.7	46.7–82.0
Choong and Roberts (21)	198	86	112	43.4	36.7–50.4
Kakourou <i>et al.</i> (22)	110	60	50	54.5	45.2–63.5
Braue <i>et al.</i> (23)	30	17	13	56.7	39.2–72.6
Dohil <i>et al.</i> (24)	302	145	155	48.0	42.4–53.6
Tabari <i>et al.</i> (18)	21	13	8	61.9	40.9–79.2
Kuchabal <i>et al.</i> (25)	100	62	38	62.0	52.2–70.9
Osio <i>et al.</i> (26)	648	330	318	50.9	47.1–54.8

Table 4. Association between swimming and MC

References	Controls (num)		MC positive (num)		Relative risk	95% CI
	Sample	History of swimming	Sample	History of swimming		
Postlethwaite <i>et al.</i> (27)	1848	915	13	13	–	–
Niizeki <i>et al.</i> (15)	24	4	24	12*	2.0	1.25–3.20
Castilla <i>et al.</i> (20)	6995	5925	517	481	2.3	1.65–3.21

–, missing data.

*High frequency swimming pool use.

found an association between having more severe MC (>26 lesions) and a range of swimming-pool-based activities, such as using a school swimming pool (RR 1.86 CI 1.79–3.37), sharing a bath sponge (RR 2.79 CI 1.69–5.43), and sharing a bath towel (RR 1.57 CI 1.33–3.67) with someone infected with MC.

Association with atopic dermatitis

Three studies suggest an association between atopic dermatitis (AD) and MC. A case-control study in Greece identified 110 children with MC and compared prevalence of AD in this group to the prevalence of AD in a previous national cross-sectional study. In the MC cohort, 18.2% ($n = 20$) had AD compared with just 5% in the national survey (22). In North America, the case notes of children attending paediatric outpatient clinics were prospectively reviewed ($n = 302$), and these showed a prevalence of AD in children with MC of 24% (24). In a similar study in France, the prevalence of AD was 43% (26).

A prospective observational study in a paediatric outpatient clinic in Brazil found no relationship between MC and the development of AD (28).

Transmission between family members

Only one study described the incidence of MC in family members of an index case. Eight children in North America were followed up for the duration of their lesions. Over an average of

at least 10 months, the researchers identified two new cases in family members (29).

Duration of lesions

Very little data on the duration of lesions was found. Two small studies in Alaska ($n = 13$) and Fiji ($n = 14$) reported a duration that ranged from 2 weeks to 24 months (29). Only in Fiji, the mean duration was calculated as 8 months (30).

Quality of life

One small study ($n = 30$) examined the impact of MC on quality of life in children with MC and their parents. Parents were significantly more concerned about MC than their child, with 82% of parents ($n = 23$) stating 'it concerned them moderately or greatly', compared with 43% of children (23).

Discussion

Summary

The largest incidence of MC is in children aged between 0 and 14 years. Combining data from different studies, we found an overall incidence rate in children of 12–14 episodes per 1000 person years. Incidence rates in the UK were greatest in those aged 1–4 years, and there was little variation between genders

(8,9). Current rates have not been explored to describe recent trends or to provide a detailed analysis of age groups within those aged 0–14 years.

We found an overall reported prevalence of MC in children of between 5.1% and 11.5%. Where gender of those attending specialist dermatologists were examined, there was little variation in numbers between males and females.

Strengths and limitations

This review has some limitations. The data collection methods used to capture a diagnosis of MC varied considerably in two studies in Japan; these may be overestimate of the point prevalence due to the self-reporting of a diagnosis. One study includes any previous diagnoses and relies upon accurate recall by parents (19), and the second did not report how a diagnosis of MC was obtained (15). Where a robust diagnostic method consisting of two independent dermatologist examinations was used, it only included children aged between 6 and 12 years and therefore did not include those at greatest risk [younger than 4 years (as shown in incidence section)]. The results of the meta-analysis may also be skewed by the three studies reporting a much higher prevalence of MC.

All studies on the incidence of MC used routinely collected data and this is subject to coding problems and under-ascertainment (2,4,31–38). Therefore, the true incidence of MC is likely to be considerably higher than that reported in these studies. This is supported by the reported prevalence, especially in studies that involved examinations, compared with the reported incidence. The difference between the incidence of MC reported in Western Europe and North America may be due to the different health-care systems in the two countries; the Western Europe studies recorded data where patients had visited a general practitioner, which is the first point of contact for all nonemergency patients. Data extracted in North America included only outpatient visits to a specialist physician, which were exclusive to the American Indian/Alaska Native population, and also are not representative of the North America population.

The association between MC and AD is not well described, and comparisons between the two are limited. Where the number of children with AD in a cohort of MC cases were compared with that of a national survey (22), they did not allow a direct comparison due to the different age groups; the national survey examined children aged 1–6 years, whereas the cohort of children attending the dermatology clinics was aged between 8 months and 11.5 years.

Where swimming pool activities such as using a school swimming pool, the sharing of towels and bath sponges with someone infected with MC were shown to increase the risk of having a more aggressive infection of MC, the analysis included both adults and children (21). As the risk factors described would typically only be associated with school-aged children who are more at risk of developing MC, the results might have been skewed.

Comparison with existing literature

Swimming was firstly discussed by Wilson (1910) as an activity causing an increased opportunity for transmission of MC (39). Since 1910, the associations between swimming and a higher risk of MC development have been described frequently within the literature. Postlethwaite *et al.* (27), Niizeki *et al.* (15), Castilla *et al.* (20), and Choong and Roberts (21), all showed that swimming was common in those with MC. Where RR has been calculated, it shows that it is likely that swimming is a causal factor for development of MC.

Climate is often described as being a factor associated with a higher prevalence of MC (40–43), and similarly, the two highest rates found in our search were in hot climates. However, the first study was described as taking place during an epidemic and the second had large variation in prevalence between individual villages and therefore it can be questioned whether the results of either are representative of warm, dry areas. Indeed, studies from other warm and dry climates such as Mali (3.6%) (16), Turkey (1.2%) (17) and Iran (2.1%) (18) have reported considerably lower prevalence.

The typical duration of lesions described in literature ranges considerably from several months to 5 years (2,41,43,44). However, during our search, we only found two studies, of small sample size, to have followed up cases of MC to describe the duration of lesions. They ranged from 2 to 24 months and an average duration of 8 months.

Implications for practice and research

Data on the epidemiology of MC is of poor quality and this may be due, in part, to MC often being considered to be a trivial condition (2). Clinicians should advise parents that MC appears to be most common in the 1- to 4-year age group and that it is more common in children with eczema and who swim. There are little data on the natural history but the best available data suggest that lesions last anywhere from 2 months to 2 years.

Further research should better define the prevalence of MC by conducting community studies involving direct examination or by using parental diagnosis if this can be shown to be of sufficient accuracy. Larger prospective studies should explore the presentation, current management, transmission, impact on quality of life and natural history of MC.

Declaration

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Ethical approval: it was not required to undertake this review.

Conflict of interest: none.

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1.2 Development and Validation of MCDTP: diagnostic accuracy study in primary care.

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Research

Jonathan R Olsen, John Gallacher, Vincent Piguet and Nick A Francis

Development and validation of the Molluscum Contagiosum Diagnostic Tool for Parents:

diagnostic accuracy study in primary care

Abstract

Background

Molluscum contagiosum (MC) is diagnosed by its distinct appearance. Parental diagnosis of MC may reduce anxiety and lead to reductions in healthcare consultations, and may be particularly useful in large-scale epidemiological studies. However, there are currently no published, validated tools allowing parental diagnosis of MC.

Aim

To develop and validate a tool for parental diagnosis of MC.

Design and setting

The Molluscum Contagiosum Diagnostic Tool for Parents (MCDTP) was developed and its diagnostic accuracy was compared with GP diagnosis in 12 GP surgeries in South Wales.

Method

Following development, which involved three phases with dermatologists, nurses, GPs, and parents, parents completed the MCDTP (index test) in the practice waiting room, and rated their confidence in their diagnosis. A GP then examined their child for MC (reference test). Test characteristics were calculated for all responders and for those who expressed being confident or very confident in their diagnosis.

Results

A total of 203 parents completed the MCDTP. The MCDTP showed a sensitivity of 91.5% [95% confidence intervals (CI) = 81.3 to 97.2] and a specificity of 88.2% [95% CI = 81.8 to 93.0] in all parents and a sensitivity of 95.8% [95% CI = 85.7 to 99.5] and a specificity of 90.9% [95% CI = 83.9 to 95.6] in parents who were confident or very confident in their diagnosis. The positive predictive value was 76.1% [95% CI = 64.5 to 85.4] and negative predictive value was 96.2% [95% CI = 91.4 to 98.8] for all parents.

Conclusion

The MCDTP performed well compared with GP diagnosis and is suitable for clinical use by parents and in population-based studies.

Keywords

dermatology; diagnostic tool; epidemiology; general practice; molluscum contagiosum; paediatrics.

INTRODUCTION

Molluscum contagiosum (MC) is a common skin condition that affects people of all ages, but is most prominent in children and the immunocompromised,¹⁻⁵ and is one of the 50 most prevalent diseases globally.⁶ In children, MC is typically diagnosed in primary care following a clinical examination by a GP. MC typically has a distinct appearance of one or more umbilicated, smooth, flesh-coloured, dome-shaped lesion/s.⁷ Unusual and more severe cases may be referred to a dermatologist.⁸

Although lesions are generally self-limiting, they can be extensive, cause itching and discomfort for children and anxiety for their parents, can result in scarring, and are sometimes treated with cryotherapy and other destructive modalities. They are also a frequent reason for parents to consult in primary care. In children there is an annual episode incidence rate between 95 and 172 per 10 000 population aged 1 to 14 years.⁹

Parents increasingly use the internet to try to diagnose skin lesions such as MC in their children. However, there are no published data on the validity of parental self-assessment. Tools using medical illustrations and text have been developed successfully to allow non-clinicians to screen for psoriasis,¹⁰ and a range of other skin lesions.^{11,12}

This study describes the development, using images and text, and validation of the

Molluscum Contagiosum Diagnostic Tool for Parents (MCDTP).

METHOD

Development of the diagnostic tool

The development of the MCDTP was in three phases.

Phase 1: Establishing the key visual diagnostic characteristics of MC. Nine dermatologists, acting as key informants, were recruited to participate in semi-structured interviews to establish the key visual and descriptive diagnostic characteristics of MC. The results from the interviews were thematically grouped into four categories: history and population, appearance, site, and symptoms. The dermatologists all reviewed a selection of photographs of MC, extracted from the Cardiff and Vale University Health Board medical image library, and four of these were selected as providing a good representation of the key visual features associated with MC lesions.

Phase 2: Generating the text. Data from phase 1 were used to draft text to accompany the images. Semi-structured interviews were then conducted with a lay parent, a school nurse, and a dermatologist specialist nurse, to modify the text to ensure that it was understandable by a lay audience, without changing the meaning.

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How this fits in

Molluscum contagiosum is a common condition where the presentation, burden, and prognosis are not well described. It is becoming more common for parents to use online descriptions and photographs to make a diagnosis; however, none of these has been measured to compare their accuracy with diagnosis by a clinician. This article describes the development of a tool to aid parental diagnosis of molluscum contagiosum, and demonstrates that it performed well compared with GP diagnosis. The tool is available online and in paper format, and can be promoted for use by parents, used by healthcare professionals, and used for education and training, and recruitment into research studies.

Phase 3: Piloting the MCDTP. To ensure that the draft of the MCDTP was usable and acceptable, 11 members of a local parent network were asked to review the document and comment on any aspects that were unclear, and to give their views on whether they thought this tool was likely to be acceptable and useful to parents. All parents taking part in this pilot thought that it would be a useful tool, and no concerns or

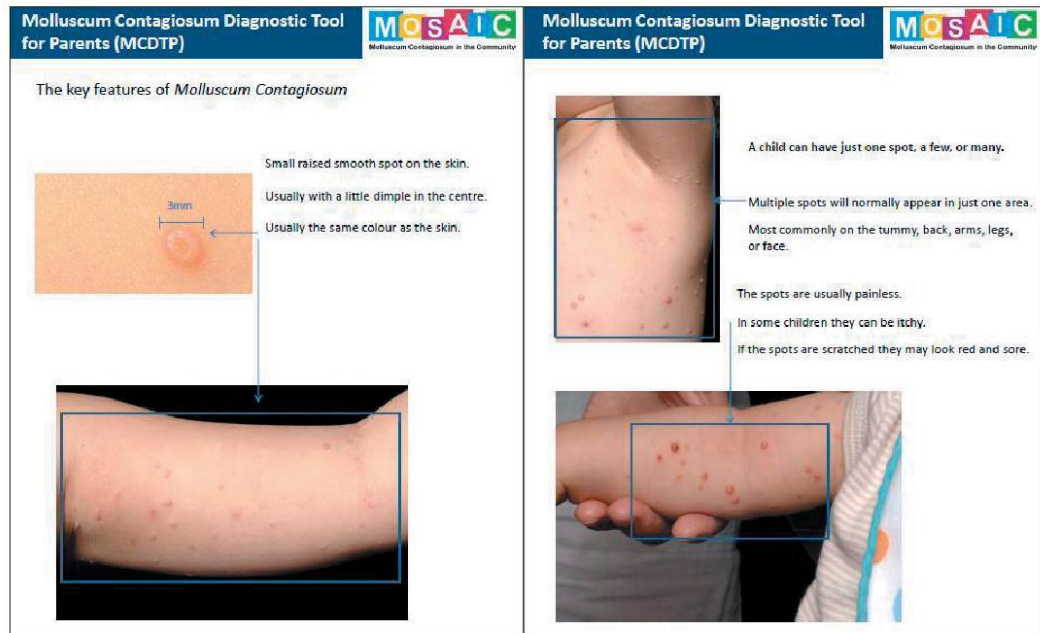
problems were identified. The final MCDTP is shown in Figure 1.

Validation of the diagnostic tool

Study population. A letter was sent to all general practices within Cardiff and Vale Health Board inviting them to take part in the study; 12 [of 93] practices responded. The aim was to include children aged 1 to 14 years consulting with a participating GP and currently having a skin lesion, as reported by their parent. Children were screened by practice reception staff or a researcher by asking the parent about the child's age and whether they had 'a spot, lump or bump on the skin'. Children were excluded if they currently or had previously had a diagnosis of MC. The parents of eligible children were asked to provide informed consent to participate.

Test methods. Participating parents were asked to use the MCDTP (the index test) in the practice waiting area prior to their consultation with a GP. Once they had determined whether their child had MC or not, they were asked to record this, and how confident they were in their diagnosis on a scale of 'very confident', 'confident', 'a bit confident', or 'not confident', on the form containing the MCDTP. During

Figure 1. Molluscum Contagiosum Diagnostic Tool for Parents. ©Cardiff University 2013.



the subsequent consultation, a clinical examination of the lesion was performed by their GP (the reference test), who noted a yes/no diagnosis of MC. Index and reference tests were performed on the same day.

Photographs of 20 participants' skin lesions (10% of the total sample) were obtained. Two consultant dermatologists and one further academic GP, with an expertise in dermatology, independently reviewed these photographs to measure agreement between the MC diagnoses given by the reference standard [GP]. Photographs were categorised by each independent observer as 'MC positive', 'probably MC', 'probably not MC', or 'MC negative'. For the analysis of inter-observer agreement, the categories 'probably MC' and 'probably not MC' were combined with 'MC positive' and 'MC negative', respectively.

Statistical methods. Sensitivity, specificity, positive predictive value, and negative

predictive value of the MCDTP diagnosis against the reference test diagnosis were calculated. Inter-rater agreement between GP and consultant dermatologist diagnosis was also calculated. Statistical analysis was performed using Stata (version 12).

RESULTS

Sixty GPs across the 12 practices participated in the study. A total of 203 parents of children aged 1–14 years completed the MCDTP between January and October 2013. Participants were evenly distributed between the sexes (47% were boys, $n = 96$) and the majority were aged 1–3 years (40%, $n = 81$) (Table 1).

The incidence of MC in this population of children consulting with a GP, and identified by their parent as having a spot, lump or bump on the skin, was 30.5%. The sensitivity, specificity, positive and negative predictive values are given in Table 2. Data on confidence in their diagnosis were provided by 186 parents, and of these 85% ($n = 158$) indicated that they were either 'very confident' or 'confident' in the diagnosis of the child's skin lesion. Greater parental confidence in their diagnosis was positively associated with agreement between parental and GP diagnoses ($\chi^2 = 26.6$, degrees of freedom = 3, $P < 0.005$), and the test performance characteristics improved when the analysis was restricted to this group (Table 2).

Photographs of lesions were obtained for 20 children; however, one was not of sufficient quality to be used because it was out of focus, and therefore 19 were available for the analysis. Diagnostic agreement was high, with κ statistics ranging from 0.71 between all clinicians and 0.79 between the expert GP and dermatologists (Table 3).

DISCUSSION

Summary

A diagnostic tool was developed for parental diagnosis of MC, and diagnosis by parents using the tool compared well with clinical diagnosis, with a sensitivity and specificity of 95.8% and 90.9% in the 85% of parents ($n = 158$) who indicated confidence in their diagnosis. The tool was especially good at ruling out MC (a negative predictive value of 96.2% in all patients and 98.0% in those who were confident in their diagnosis).

Strengths and limitations

The development of this tool involved a comprehensive process that involved multiple key stakeholders. In particular, the language used in the tool needed to be

Table 1. Participant characteristics

Age, years	Sex, n (%)		Total, n (%)
	Boys	Girls	
1–3	36 (44)	45 (56)	81 (40)
4–6	25 (46)	29 (54)	54 (27)
7–9	19 (53)	17 (47)	36 (18)
10–14	16 (50)	16 (50)	32 (15)
Total	96 (47)	107 (53)	203 (100)

Table 2. Incidence of molluscum contagiosum, and sensitivity, specificity, positive predictive value, and negative predictive value for the Molluscum Contagiosum Diagnostic Tool for Parents

a) All participants regardless of confidence in diagnosis ($n = 203$)		
	%	95% CI
Incidence of MC	30.5 ($n = 62$)	22.9 to 35.8
Sensitivity	91.5	81.3 to 97.2
Specificity	88.2	81.8 to 93.0
Positive predictive value	76.1	64.5 to 85.4
Negative predictive value	96.2	91.4 to 98.8
b) Participants who indicated they were 'very confident' or 'confident' in their diagnosis ($n = 158$)		
	%	95% CI
Incidence of MC	30.4 ($n = 48$)	23.3 to 38.2
Sensitivity	95.8	85.7 to 99.5
Specificity	90.9	83.9 to 95.6
Positive predictive value	81.2	69.9 to 91.1
Negative predictive value	98.0	93.1 to 99.8

MC = molluscum contagiosum.

Table 3. Inter-rater agreement between reference standard, GP and two dermatologists where probable and confirmed diagnosis are merged

Diagnosis of photographs (n = 19)	Agreement (%)	κ statistic	95% CI	Strength of agreement ¹³
a) Agreement between GP and diagnosis made by clinician viewing image				
GP expert	94.7	0.78	0.35 to 1.0	Substantial
Dermatologist 1	89.5	0.61	0.14 to 1.0	Substantial
Dermatologist 2	84.2	0.5	0.43 to 0.95	Moderate
b) Agreement between clinicians viewing images				
	89.5	0.79	0.74 to 0.8	Substantial
c) Agreement between all clinicians (reference test and those viewing images)				
	84.2	0.71	0.56 to 0.72	Substantial

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Ethical approval

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Provenance

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Competing interests

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understood by a lay audience, as even the most commonly used medical terminology should be carefully explained to parents to avoid confusion.¹⁴ A high level of agreement was found between clinicians, suggesting that the gold standard diagnosis was likely to be accurate. However, diagnosis was not able to be confirmed either histologically or by diagnosis by an expert dermatologist as this would have been expensive, burdensome to patients, and may have discouraged participation. However, high levels of agreement were found between GP diagnosis and the diagnosis made by a panel of experts, suggesting that GP diagnosis is likely to be reliable. The initial design of the MCDTP was also piloted to ensure the instructions and wording of the tool were clear and that it was acceptable to its target population.¹⁵

Sufficient numbers were included to allow a reasonable degree of precision around estimates. There are no data on how likely parents are to respond positively to the screening question 'Does your child have a spot, lump, or bump on the skin?' or the diagnostic accuracy in an unscreened population.

Comparison with existing literature

There are no known studies of tools for assisting parents in making a diagnosis of MC in their children. However, tools to help patients self-diagnose other skin conditions have been evaluated. The Psoriasis Screening Tool was found to have a high sensitivity and specificity of 96.4% (95% confidence intervals (CI) = 93.2 to 98.0) and 97.3% (95% CI = 94.1 to 98.9), respectively, when compared with dermatologist diagnosis.¹⁰ A study exploring the diagnostic accuracy of self-diagnosis of a variety of skin lesions through the use

of 12 lesion images and matching them to a correct diagnosis using diagnostic support software found that non-clinicians (n = 23) correctly diagnosed 96% of lesions (231 out of 240). When this was compared with medical students (n = 27) who had recently completed a 2-week dermatology attachment, and did not use diagnostic support software, their diagnostic accuracy was found to be considerably lower, 51% (160 out of 312).¹¹

Using a standardised questionnaire to measure the presence of skin disease in both a health-seeking (n = 99) and non-health-seeking population (n = 98), it provided a best sensitivity and specificity of 61% and 69% compared with a dermatologist.¹⁶ This instrument was designed to measure presence of skin disease in the population and did not identify specific conditions. Although it has a relatively low accuracy in measuring the presence of a skin condition, the authors noted that further development was required before use in a large epidemiological study.

Overall the agreement between the clinician's diagnosis and reference standard in the current study was substantial to moderate. Previous studies show agreement between a primary care physician's diagnosis of MC and a dermatologist as correct in 100% of cases;^{17,18} however, these were in small studies (n = 8 and n = 3) where each rater saw the patient face to face.

The results of this study show that, although photographs alone can be effective in providing a diagnosis, in 35% of cases this was not alone sufficient to make a definitive diagnosis. It is not known how much of the observed disagreement is related to the photographs, as there may well be disagreement even when both clinicians examine the child. This is similar to other studies of much larger numbers where 20% of dermatologists did not provide a single diagnosis using only photographs, although dermatologists were able to provide a definitive diagnosis in significantly more cases during face-to-face consultations.¹⁹ High levels of diagnostic agreement were found, which are comparable to other studies where agreement ranged between 81% and 89%.¹⁹ Warshaw *et al.*²⁰ conducted a systematic review of teledermatology diagnosis agreement between a dermatologist following a face-to-face consultation, and a second using only photographs; this provided a weighted average agreement of 65.3%. In a study where a similar number of patients were assessed (n = 16), the κ coefficient of dermatologist agreement was similar to the

current study data when combining all four clinicians' diagnoses ($\kappa = 0.67$),⁹ Warshaw *et al*²⁰ showed the overall κ coefficient in a number of studies ranging from 0.65 to 0.87.

Implications for research and practice

The main aim of this study was to develop and validate a tool for use in an epidemiological study; and the data suggest that the MCDTP is suitable for this purpose. Although self-diagnosis using pictures and text is common, the validity of this has not previously been assessed. As MC is a self-limiting condition, the MCDTP could

be an appropriate screening tool for use by parents in the community. It is available online (www.molluscum-info.com), and healthcare practitioners and organisations are encouraged to promote use of the site and provide a link on their websites. The site could also be used for education and training purposes, and the website and/or paper tool could be used to identify suitable patients for inclusion in studies on MC. Factors such as parent confidence in their diagnosis can be incorporated into epidemiological studies or primary care screening tools if a higher accuracy was required.

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1.3 Time to resolution and impact on quality of life of molluscum contagiosum in children: a prospective community cohort study.

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Time to resolution and effect on quality of life of molluscum contagiosum in children in the UK: a prospective community cohort study

Jonathan R Olsen, John Gallacher, Andrew Y Finlay, Vincent Pigué, Nick A Francis

Summary

Background Molluscum contagiosum is one of the 50 most prevalent diseases worldwide, but scarce epidemiological data exist for childhood molluscum contagiosum. We aimed to describe the time to resolution, transmission to household child contacts, and effect on quality of life of molluscum contagiosum in children in the UK.

Methods Between Jan 1, and Oct 31, 2013, we recruited 306 children with molluscum contagiosum aged between 4 and 15 years in the UK either by referral by general practitioner or self-referral (with diagnosis made by parents by use of the validated Molluscum Contagiosum Diagnostic Tool for Parents [MCDTP]). All participants were asked to complete a questionnaire at recruitment about participant characteristics, transmission, and quality of life. We measured quality of life with the Children's Dermatology Life Quality Index (CDLQI). Participants were prospectively followed up every month to check on their recovery from molluscum contagiosum and transmission to other children in the same household, until the child's lesions were no longer visible.

Findings The mean time to resolution was 13·3 months (SD 8·2). 80 (30%) of 269 cases had not resolved by 18 months; 36 (13%) had not resolved by 24 months. We recorded transmission to other children in the household in 102 (41%) of 250 cases. Molluscum contagiosum had a small effect on quality of life for most participants, although 33 (11%) of 301 participants had a very severe effect on quality of life (CDLQI score >13). A greater number of lesions was associated with a greater effect on quality of life ($H=55·8$, $p<0·0001$).

Interpretation One in ten children with molluscum contagiosum is likely to have a substantial effect on their quality of life and therefore treatment should be considered for some children, especially those with many lesions or who have been identified as having a severe effect on quality of life. Patients with molluscum contagiosum and their parents need to be given accurate information about the expected natural history of the disorder. Our data provide the most reliable estimates of the expected time to resolution so far and can be used to help set realistic expectations.

Funding Wales School of Primary Care Research (WSPCR) and Cardiff University.

Introduction

Molluscum contagiosum is a common skin disorder that affects mainly children^{1,2} and is one of the 50 most prevalent diseases worldwide.³ Molluscum contagiosum has the greatest incidence in individuals aged 1–14 years;⁴ prevalence in children is between 5% and 11%.⁵ Scarce data exist for the time to resolution of the disorder and as a result, guidance documents tend to be vague and conflicting.^{6–9} Previous evidence suggests that lesions last between 2 weeks and 24 months,^{10,11} but these studies were in very small samples from highly culturally specific populations. Molluscum contagiosum is transmitted between human hosts by the infectious matter discharged from the lesions¹² and epidemics have been described in New Guinea¹³ and Israel.¹⁴ However, little evidence exists of transmission between children living within the same household; one small study in Alaska ($n=13$) described further cases in two (25%) of eight households.¹¹ The most recent Cochrane review of treatments for cutaneous molluscum contagiosum recommended no active treatment.¹⁵ However, although

the disorder is deemed trivial by some clinicians,⁸ little is known about its effect on quality of life. To understand more fully the time to resolution, transmission pattern, and quality of life effect of molluscum contagiosum in children, we did a prospective cohort study in a UK community sample.

Methods

Case definition

From Jan 1 to Oct 31, 2013, children aged 4–15 years at recruitment, residing in the UK, and with a clinical or parental diagnosis of molluscum contagiosum, were invited to participate in the study by two referral routes: clinical or self-referral. For clinical referral, general practice (GP) clinics ($n=16$) and dermatology outpatient clinics ($n=3$) in Wales, UK, acted as participant information centres. When a child was diagnosed with molluscum contagiosum by a doctor, they were given a card informing them of our study. To receive more information, the parent was asked to provide their name and contact information (telephone number or email address) and return it to the research team.

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For self-referral, potential study participants were informed of the study through media advertisement and posts within health forums such as Mumsnet and Netmums (health forums are independent websites that provide an online network for parents where they can post and share parenting information¹⁶). Additionally, advertisements were placed through the online search engine Google with Google AdWords. The advertisement was triggered by the search terms “molluscum”, “contagiosum”, and “child” or “children”. A short newspaper article was published in a Welsh national newspaper,¹⁷ and parents of children attending 159 local primary schools in South Wales, UK, were emailed information about the study.

Parents who thought their child might have molluscum contagiosum were directed to the study website, where they were asked to confirm the diagnosis by using the Molluscum Contagiosum Diagnostic Tool for Parents (MCDTP). The MCDTP is a two page document that uses images and text to enable a parent to identify whether their child's skin lesions are molluscum contagiosum. The MCDTP has been validated for use by parents (92% sensitivity and 88% specificity) and was compared with a clinical diagnosis.¹⁸ If use of the MCDTP did not confirm diagnosis of molluscum contagiosum, the parent was not invited to participate in the study.

Data collection

All participants were asked to complete a questionnaire at recruitment (online or paper) asking about participant characteristics, transmission, and quality of life. Quality of life was measured with the Children's Dermatology Life Quality Index (CDLQI), which is the most widely used dermatology specific measure for children with dermatological disorders.¹⁹ The CDLQI questionnaire has ten questions about the effect of a skin disease on the life of the affected child over the past week.¹⁹ The questions were developed on the basis of interviews with large numbers of children with various skin diseases. The topics covered include symptoms, embarrassment, friendships, clothes, playing, sports, school, bullying, sleep, and effect of treatment. The questionnaire has been validated for many disorders including atopic eczema and molluscum contagiosum.²⁰

Follow-up

Participants were prospectively followed up every month to check on their recovery from molluscum contagiosum and transmission to other children (aged <14 years) in the same household, until the child's molluscum contagiosum lesions were no longer visible. Follow-up was done by email or text message, depending on the parents' stated preference, with one reminder sent after 7 days to those who failed to respond. Parents who failed to complete the follow-up or respond to the study team for 2 consecutive months were deemed to be lost to follow up and were not contacted again by the study team.

Data analysis

The primary study outcomes were time to resolution, transmission to family members, and dermatology specific quality of life (measured with the CDLQI). Time to resolution was measured by the number of months that the lesions were present; the event start date was the date lesions were initially present and resolution measured as the point lesions were no longer visible. We calculated descriptive statistics for all outcomes. We described distributions with the mean or median and the standard deviation (SD) or the first and third quartiles (Q₁ and Q₃) or the range, depending on the distribution. The data from the CDLQI scores are positively skewed and no transformation was adequately able to improve the fit of normality, so we used a non-parametric Kruskal-Wallis test to compare the medians for the predictor variables with two or more levels. We calculated survival estimates with Kaplan-Meier statistics. We used hazard ratios to show whether sex, having an affected family member, treatment (prescribed or non-prescribed), an increased number of lesions, or referral method affected the time to resolution. Data from participants lost to follow-up were censored at the first incomplete follow-up time point; data for those who had not recovered by the end of the study were censored at the study end date. We restricted transmission analysis (as a proportion) between family members to only those living with family members aged younger than 14 years. We did statistical analyses with STATA (version 12).

Ethical approval was obtained by NRES Committee South Central—Berkshire B (12/SC/0455). Research governance approval was granted by Cardiff and Vale University Health Board (NISCHR-PCU [100161]).

For the CDLQI see <http://www.dermatology.org.uk/quality/cdlqi/quality-cdlqi-questionnaire.html>

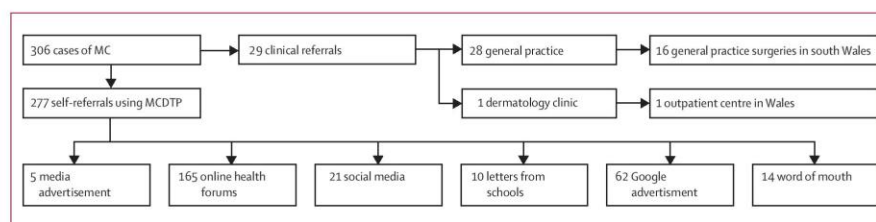


Figure 1: Source of recruitment for study participants

	N
Age (years)	
Mean	6.7 (2.4)
Median	6 (5–8)
Range	4–15
Sex	
Boys	139 (45%)
Girls	167 (55%)
Presentation	
Number of molluscum contagiosum lesions	
1	21 (7%)
2–5	55 (18%)
6–10	56 (18%)
11–15	48 (16%)
16–20	50 (16%)
≥21	76 (25%)
Location of lesions (many responses available)	
Legs	157 (51%)
Torso	152 (50%)
Arms	150 (49%)
Armpits	69 (23%)
Back	62 (20%)
Genitals	53 (17%)
Buttocks	51 (17%)
Face	49 (16%)
Neck	47 (15%)
Hands	13 (4%)
Feet	12 (4%)
Most frequent pairs of locations	
Torso and arms	99 (32%)
Torso and legs	86 (28%)
Arms and legs	75 (25%)

Data are n (%), mean (SD), or median (IQR), unless stated otherwise.

Table 1: Participant characteristics (n=306)

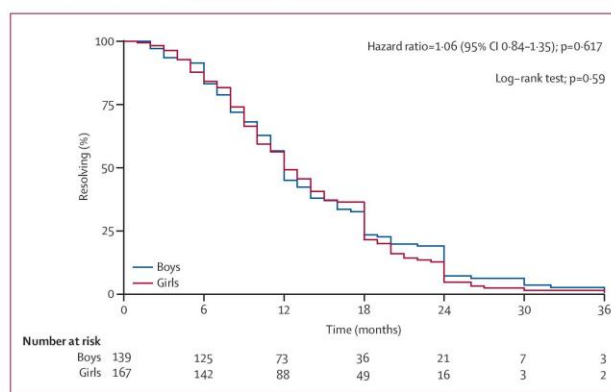


Figure 2: Kaplan-Meier survival estimates of time to resolution by sex

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

306 parents were recruited and completed the baseline questionnaire. 277 (90.5%) participants were recruited by self-diagnosis with the MCDTP via the study website, with 28 (9.2%) referred from primary care and one (0.3%) referred from a dermatology outpatient clinic. Figure 1 shows the recruitment of participants through each campaign.

The 306 participants were aged between 4 and 15 years, with a mean of 6.7 (SD 2.4) years. There were slightly more girls (55%) than boys and nearly a quarter (76/306) of children had 21 or more lesions, which were widely distributed over the body, but mostly on legs and arms (table 1). The most common pair of locations were the torso and arms (table 1). Nearly 214 [70%] of 306 children had lesions in more than one site and 86 (24%) of 306 children with data available described the presence of atopic eczema. 58 (19%) parents reported that their child had received treatment for their molluscum contagiosum. However, for a third of children (18/58), this was treatment with topical antibiotics, and therefore presumably treatment for complications rather than the molluscum contagiosum per se. Only one patient had been treated with curettage and one patient had been treated with 5% potassium hydroxide solution. All covariants were complete and there were no missing data.

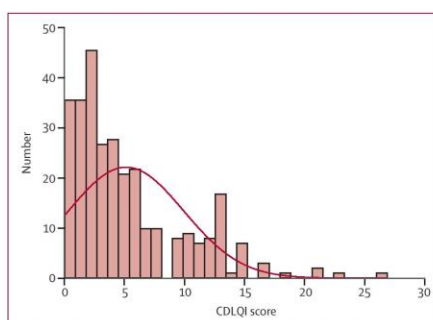
Complete follow-up data were available for 269 (88%) of 306 children, with 21 (8%) of these patients not recovering by study end. For those with complete follow-up data, the mean time to resolution was 13.3 months (SD 8.2, median 12 [IQR 8–18], range 1–62 months). 156 (58%) of 269 children had recovered by 12 months, 80 (30%) still had lesions at 18 months, and 36 (13%) had lesions that persisted at 24 months.

Time to resolution did not differ by sex (figure 2). We recorded no associations between the time to resolution of lesions and self-reported receipt of prescription medication, self-medication, having an affected family member, or a greater number of lesions at recruitment (table 2). However, time to resolution was significantly shorter in those who self-referred (mean 8.9; 95% CI 6.4–11.4 months) than in those who were referred by a clinician (mean 13.3; 95% CI 12.3–14.2 months; table 2).

CDLQI data were available for 301 (98%) of 306 participants. The distribution of CDLQI scores was positively skewed with a median of 4 (IQR 2–7) and mean of 5.1 (SD 4.8; figure 3), suggesting a small effect on quality of life for most patients.²¹ However, 85 (28%) participants reported at least a moderate effect on quality of life

	Hazard ratio (95% CI)	p value
Sex	1.06 (0.84–1.35)	0.617
Prescribed drugs (reported)	1.29 (0.94–1.77)	0.112
Self-treatment (reported)	1.13 (0.88–1.44)	0.344
Affected family member	1.22 (0.93–1.60)	0.141
Number of lesions (≥ 21 at baseline)	0.95 (0.58–1.56)	0.843
Referral method (self or clinical)	0.58 (0.34–0.98)	0.040

Table 2: Associations with time to resolution

Figure 3: Distribution of CDLQI scores
CDLQI=Children's Dermatology Life Quality Index.

(CDLQI score >7) and 33 (10%) participants reported having a large effect on quality of life (CDLQI score >13) from their molluscum contagiosum. We recorded no association between quality of life and presence of atopic eczema. However, being a girl, greater duration of lesions at baseline, and number of lesions were all positively associated with higher CDLQI scores (greater quality of life impairment) at baseline (table 3).

250 (82%) of 306 participants indicated that there was more than one child aged 14 years or younger living in the household. Of those with multiple children living in the same household as an index case, 102 (41%) of 250 indicated that one or more had developed molluscum contagiosum during follow-up (ie, before the index case's lesions had resolved). The severity (number of lesions) of molluscum contagiosum in the index case at baseline was not associated with risk of transmission to cohabiting children ($\chi^2(df\ 5)\ 6.3\ p=0.28$).

Discussion

This is the largest reported prospective cohort of children with molluscum contagiosum. Most children have the disorder for 12 months, and experience a small effect on their quality of life. However, our findings show that a substantial proportion of children with molluscum contagiosum have lesions for a long period, which has a large effect on quality of life. High numbers of lesions and long duration of lesions are associated with greater impairment in quality of life.

	N	Median (IQR)	H, p value
CDLQI scores			
Mean (SD)	5.1 (4.8)	4 (2–7)	
By sex			12.8, 0.0003
Boys	137	3 (1–6)	
Girls	164	4 (2–9)	
Referral method			0.34, 0.5603
Clinical referral	29	4 (2–8)	
Web referral with MCDTP	272	4 (1–7)	
By presence of atopic eczema			0.76, 0.3785
Eczema present	84	4 (2–9)	
No previous eczema diagnosis	217	4 (2–7)	
By number of lesions			55.8, <0.0001
1	20	2.5 (0–5)	
2–5	55	2 (1–5)	
6–10	56	2 (1–5)	
11–15	46	4 (2–7)	
16–20	49	3 (2–7)	
≥ 21	75	7 (4–13)	
By duration of lesions (at baseline)			4.65, 0.3256
<1 month	47	2 (2–5)	
1–2 months	
3–4 months	48	4 (2–7)	
5–6 months	41	4 (1–8)	
6–12 month	74	4 (2–8)	
>12 months	91	4 (1–9)	

Double dots show no children in this group. CDLQI score ranged from 0 to 27.
CDLQI=Children's Dermatology Life Quality Index. MCDTP=Molluscum Contagiosum Diagnostic Tool for Parents.

Table 3: CDLQI scores at recruitment

Uniquely, we used a validated diagnostic method for molluscum contagiosum that allowed recruitment directly from the community, without the need for expensive and inaccessible clinical assessments,^{22,23} which makes our sample more representative of cases of molluscum contagiosum in the UK than studies that rely on recruitment in clinical settings. Additionally, MCDTP has high sensitivity and specificity when used by parents.¹⁸

Although recruitment through various novel methods such as health forums and online search engines generate many participants, these approaches can result in different selection biases. We noted differences in the mean time to resolution of symptoms between those who were self-referred to the study and those referred by a clinician, suggesting that the sample referred by clinicians might represent more severe cases. However, we noted little difference in CDLQI scores between those recruited by the two approaches. Less severe cases of molluscum contagiosum are less likely to be detected than are more severe cases with either approach;

Panel: Research in context**Systematic review**

We published a systematic review in December, 2013, containing a description of the time to resolution, transmission between family members, and quality-of-life effect of childhood molluscum contagiosum.³ With OvidSP, we searched Medline (Jan 1, 1946 to Oct 31, 2012), Embase (Jan 1, 1947 to Oct 31, 2012), and Cochrane databases, using search terms listed in the appendix. We found two studies^{13,14} that reported time to resolution of childhood molluscum contagiosum ranging from 2 weeks to 24 months. However, both studies were small (Alaska $n=13$,¹³ Fiji $n=14$ ¹⁴) and were done more than 40 years ago. One study¹³ ($n=8$) reported transmission to household contacts in 25% of children. Measuring quality-of-life impairment in children with molluscum contagiosum with the CDLQI was described in two small studies of children with seven participants¹⁹ and 14 participants;²⁵ both results showed a small average effect on quality of life.

Interpretation

This is the largest reported prospective cohort of children with molluscum contagiosum. On average it takes 13 months for molluscum contagiosum lesions in children to resolve; however, one in four children will still have lesions after 18 months and 13% will still have lesions after 24 months. Transmission between family members is common. Molluscum contagiosum seems to be highly contagious, with nearly half of the households that included additional children having transmission to one or more children. These data can be used to help inform parents and other interested stakeholders. For most children, molluscum contagiosum has a small effect on quality of life; however, one in ten children have a very severe effect on quality of life. Our findings emphasise the need to consider treatment for some children, especially those with larger numbers of lesions and those with a big effect on quality of life.

See Online for appendix

therefore, our estimate of time to resolution might overestimate the true duration. However, we found no association between severity (measured by CDLQI or number of lesions) and time to resolution.

The CDLQI is designed to measure dermatology specific quality of life irrespective of other non-skin disorders that might affect quality of life. The method allows for comparisons between patients with various skin disorders.¹⁰ However, it is unlikely to be as sensitive, responsive, and relevant to individual patients as disease-specific methods.²⁴ To address this limitation in our analysis, we provided quality of life data according to severity of disorder, age, and time to resolution. The CDLQI is completed by a child with the help of parents if necessary. Therefore, responses could have been affected by parental perception in younger children.

The prognosis of molluscum contagiosum is poorly described. Two early studies of children during the 1960s described time to resolution of between 2 weeks to 24 months collected retrospectively from interviews of family members (panel).¹¹ In the study done in Fiji, the mean time to resolution was 8 months.¹⁰ Although the range of time to resolution in both of these studies was similar to our findings, our prospectively collected data from 269 children provide a far more precise estimate and are more comprehensive. We noted no association between sex, having an affected family member, treatment (prescribed or non-prescribed) or an

increased number of lesions and time to resolution. To our knowledge, none of the patients were immunosuppressed.

We noted that a high proportion of children who had child household contacts reported spread of the disease to other children in the house. A prospective case series study of eight children diagnosed with molluscum contagiosum when visiting a physician in Alaska reported spread to family members in two new cases.¹¹

Two previous studies^{19,25} have used the CDLQI to assess the effect of molluscum contagiosum on quality of life. Both were small studies (fewer than ten participants each) of children attending dermatology outpatient clinics in the UK and suggested the disorder has a small effect on quality of life (mean CDLQI score 3.1, SD 4.9). Our data provide a similar mean CDLQI score of 5.1. High numbers of participants have allowed us to stratify quality of life effect according to severity, age, sex, and time to resolution, showing a high effect on quality of life of patients with severe molluscum contagiosum. Similarly, studies in patients with atopic eczema have shown this association.^{26–28} Findings of an Australian study ($n=30$) that did not use the CDLQI showed that parents were much more concerned about molluscum contagiosum than their child, with 82% of parents ($n=23$) stating “it concerned them moderately or greatly”, compared with 43% of children.²⁹ Although we did not assess quality of life effect on family members, results of other studies show that family members might experience psychological distress as much as, or in some cases more than, the patient.³⁰

Active treatment for molluscum contagiosum could be considered with a similar algorithm to the guidelines³¹ on psoriasis by the UK National Institute for Health and Clinical Excellence (NICE), which suggest drug regimens based on both a PASI³² and DLQI³³ score. Guidelines for molluscum contagiosum should consider a recommendation for the CDLQI score, and the number of lesions present to be taken into account when making management decisions.

In summary, molluscum contagiosum is often perceived as being a trivial self-limiting disorder by some clinicians,⁸ but our data suggest that for some children this is not the case. We found an average time to resolution of 13.3 months, but parents should be aware that for 13% of children lesions might not have resolved by 24 months. Parents with more than one child at home should be aware that there is a significant risk of spread to other children. Further research is needed to understand what steps, if any, can be taken to reduce this risk. Children with a greater number of lesions (21 or more) are most likely to have a high effect on quality of life. Therefore, the idea that molluscum contagiosum is always a benign, trivial illness needs to be challenged, and active treatment should be considered for some children, especially those with larger numbers of lesions and those with higher CDLQI

scores. Further studies are needed to assess the effect of therapeutic approaches in children with more severe molluscum contagiosum.

Contributors

JRO, JG, VP, and NAF designed the study. JRO completed the data collection, analysis and wrote the first draft of the article. All authors contributed to the data analysis plan, data interpretation and wrote the article.

Declaration of interests

AYF is joint copyright owner of the CDLQI. The other authors declare no competing interests.

Acknowledgments

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1.4 Conference abstract (MCDTP Design)

Olsen JR, Francis NA, Gallacher J, Piguet V. Designing the 'molluscum contagiosum diagnostic tool for parents' (MCDTP) (Poster). *Journal of Investigative Dermatology*, 133(S1). pp.S88.

International Investigative Dermatology Conference 2013, Edinburgh, UK.

ABSTRACTS | Epidemiology & Health Services Research

512

Systematic review of pharmacogenomics in psoriasis

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Pharmacogenetic and pharmacogenomic studies have investigated biomarkers of drug efficacy and toxicity in psoriasis, yet none have translated into clinical care. We performed a systematic review of publications assessing the influence of genetic/genomic variation on treatment response in psoriasis patients. Studies were included where: participants had a diagnosis of psoriasis; a genomic test was performed; response to treatment was documented with a defined outcome measure and treatment response was correlated with the genomic test. Four electronic databases were searched from inception to August 2012. In total 27,203 abstracts were scanned, from which 121 full papers were evaluated; only 45 studies, published between 1995 and 2012, met inclusion criteria. Therapies evaluated included 9 topical, 8 phototherapy, 8 systemic, 19 biologic and 3 novel immunotherapies. Of the 26 pharmacogenetic and 19 pharmacogenomic studies, only 2 reported undertaking a sample size calculation before patient recruitment. A positive association with efficacy or toxicity and genetics/genomics was reported by 33 studies. Sources of heterogeneity included: poor phenotyping of participants; failure to define treatment response using validated methodology; timing of measurement of response and; documentation of participants' concurrent therapies. Key quality control data were rare, including accuracy of genotyping in pharmacogenomic studies (2 of 26) and derivation of statistically significant fold change in gene expression. To realise the power of genomics in the field of personalised medicine, genomic screening prior to psoriasis therapy must be accurate and effective in predicting response and in preventing adverse reactions. Thus we recommend: high quality phenotyping of participants; publication of reproducible methodology including a priori power to detect association; use of a validated outcome measure for measurement of psoriasis and; a clear definition of response.

514

Association between the type and length of tumor necrosis factor (TNF) inhibitor therapy and myocardial infarction (MI) risk in psoriasis

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We sought to assess whether the type of TNF inhibitor therapy (soluble receptor versus monoclonal antibody) has an effect on the association of MI risk, and determine whether length of TNF inhibitor therapy has an effect on the association of MI risk. This was a retrospective cohort study from January 1, 2004 and November 30, 2010 of at least 3 ICD9 codes for psoriasis (696.1) or psoriatic arthritis (696.0) without antecedent MI. In the 3 subgroups of TNF inhibitors, 976 received etanercept only; 217 received monoclonal antibody only; and 480 received etanercept or monoclonal antibody. In the Cox proportional hazards analysis, etanercept only (HR, 0.53; 95% CI, 0.31-0.92) was associated with a significant reduction of MI risk compared to topical agents, and monoclonal antibody only (HR, 0.25; 95% CI, 0.06-1.03) and etanercept or monoclonal antibody (HR, 0.53; 95% CI, 0.27-1.06) were associated with a non-significant reduction of MI risk compared to topical agents. Using year 1 as reference, those who received TNF inhibitor therapy at year 2 (HR, 0.71; 95% CI, 0.19-2.67) had a non-significant reduction of MI risk; and those who received TNF inhibitor therapy at year 3 (HR, 1.51; 95% CI, 0.52-4.35) and at year 4 (HR, 1.25; 95% CI, 0.50-3.11) had a non-significant increase of MI risk. Treatment with etanercept compared to treatment with topical agents, was associated with a significant decreased risk of MI in psoriasis patients. Treatment with monoclonal antibody only and etanercept or monoclonal antibody, compared to treatment with topical agents, was associated with a non-significant decreased risk of MI in psoriasis patients. There was a trend that those treated with TNF inhibitors at year 3 or 4 had a non-significant increased risk of MI compared to those who were treated with TNF inhibitors at year 1.

516

Thanakha and its dermatologic uses in Myanmar (Burma)

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Recent geopolitical changes in Myanmar have resulted in new opportunities to study skin health and disease in a previously isolated population. This cross-sectional study investigated the dermatologic uses of thanakha in Myanmar. Used by Burmese people for over 2,000 years, thanakha powder is produced by grinding the bark of *Hoplostethus crenulatus* or *Naring crenulatus* trees on a round slab called a kyauk pyin. The powder is then mixed with water to form a thin yellow paste that is applied directly to the skin. We conducted semi-structured interviews with 25 Burmese persons who wear thanakha. Participants were both men and women, age 12-55, and represented three different regions of Myanmar. Nine distinct dermatologic uses were identified: photoprotection, acne treatment and prevention, skin lightening, skin cooling, aesthetics (make-up), rhytid reduction, pruritis relief, scar reduction, and odor prevention. Our study determined that in Myanmar, thanakha is being used daily for treatment and prevention of some of the most prevalent dermatologic conditions. As travel restrictions to Myanmar diminish, further research should investigate the efficacy and safety of thanakha for various dermatologic conditions.

513

Hospitalizations for cellulitis in Canada: A retrospective database study

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Background: Cellulitis is the most common skin condition responsible for emergency department visits and inpatient admissions in Canada. This study examined hospitalization records of patients admitted for cellulitis in order to determine factors associated with prolonged hospital stay and mortality, as well as health services use by these patients. Methods: Records from the national database of hospital discharges, which encompasses all hospitalizations across Canada, excluding Quebec and the territories, were analyzed. All patients from 2004-2008 with an admission diagnosis of cellulitis (ICD code "L03") were included in the study. Factors associated with mortality and prolonged hospital stay (defined as greater than 7 days) were analyzed in univariate and multivariate analysis through logistic regression and are expressed as odds ratios (OR). Results: During the five-year study period, there were 65,454 patients hospitalized for cellulitis. Majority were males (54%), and the average age at admission was 55.5 years (SD 23.9). Mortality during the admission was about 1%, and the average length of hospital stay was 7.1 days. The most common comorbid condition among patients was diabetes (8.4%), followed by congestive heart failure (3%). Consulting services were used in 39% of hospital admissions. Factors associated with prolonged hospital stay included female gender, advanced age, comorbid congestive heart failure, admission to or consultation by a surgical service, and dermatology consultation (OR 4.5, 95% 3.9-5.2). Factors associated with mortality were male gender, advanced age, the presence of any comorbidity, surgical consultation and infectious disease consultation. Interpretation: Cellulitis is responsible for a large number of hospital admissions in Canada. The elderly and patients with comorbidities are at increased risk for longer hospital stay and death. Cellulitis may represent a heterogeneous group of conditions and therefore frequently requires multidisciplinary approach as evidenced by high use of consulting services.

515

Designing the 'molluscum contagiosum diagnostic tool for parents' (MCDTP)

JS Olsen,¹ NA Francis,¹ J Gallacher¹ and V Piguet¹ ¹ Cochrane Institute of Primary Care and Public Health, Cardiff University, Cardiff, United Kingdom and ² Department of Dermatology and Wound Healing, Cardiff University, Cardiff, United Kingdom

Molluscum Contagiosum (MC), a member of the poxvirus family, is a viral disorder of the skin and mucous membranes characterised by discrete, single or multiple flesh coloured papules. The virus can lead to discomfort and pain, in children there can also be symptoms of pruritis, erythema, inflammation and super infections in some cases. Lesions are diagnosed upon sight due to their distinct appearance, in unusual and rare cases they may be referred for biopsy. This study aims to design a self diagnostic tool for parents. A two phased approach was conducted, firstly nine dermatologists were interviewed to establish the key diagnostic features of MC. Interviews were tabulated and grouped by key themes. Medical illustrations were selected, and dermatologists were asked to choose those which were most representative of typical lesions. The tabulated findings from interviews were then discussed with a patient representative, dermatology specialist and school nurse to produce clear wording in a lay language, also maintaining the key diagnostic elements. The second phase of the study piloted a draft version of the MCDTP at a local parent group (n=10) to determine whether it was clear and understandable. The following themes were identified for the diagnosis of MC: appearance, geographical site, symptoms, and natural history. A colour booklet was produced which used four images, accompanied with key text highlighting the features of MC. The MCDTP is a well designed and piloted tool to allow those without a clinical background to diagnose MC in children. The authors specifically designed this tool as a recruitment aid for a cohort of children over a large geographical area. Before the MCDTP can be used, the diagnostic accuracy of parental use needs to be determined in a validation study against a gold standard assessment. Once validated the MCDTP will also have uses for parents to allow self-diagnosis, and when accompanied with information about MC, may reduce primary care consultations for MC.

517

Alcohol intake is associated with increased risk of squamous cell carcinoma of the skin: Prospective cohort study

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The objective of this study was to investigate the association between alcohol intake and the incidence of cutaneous squamous cell carcinoma (cSCC). Multivariate Cox survival models with time-dependent exposure and covariates were used to estimate relative risks (RRs) and 95% confidence intervals (CIs) in three separate cohorts of U.S. women and men. The results were then meta-analyzed. A total of 174,998 women and 48,140 men participating in the Nurses' Health Study, Nurses' Health Study II and Health Professionals' Follow-up Study were followed for up to 28 years. Information on alcohol intake and covariates was collected at baseline and updated several times during the follow-up. During a follow-up of 4,234,416 person-years, 2,938 histopathologically verified, incident invasive cSCC and 1,590 cSCC in situ were identified. Alcohol intake was significantly associated with an increased risk of invasive cSCC in all three cohorts. A significant dose-response relationship was observed: each additional drink (12.8 gram of alcohol) per day was associated with 22% increased risk of invasive cSCC (RR 1.22, 95% CI 1.13-1.31) and with 14% increased risk of cSCC in situ (RR 1.14, 95% CI 1.04-1.26). White wine consumption ≥ 5 times a week was significantly associated with an additional risk of invasive cSCC (RR 1.31, 95% CI 1.09-1.59). The results of this large prospective cohort study indicate that even a moderate consumption of alcohol increases the risk of developing cSCC in a dose-dependent manner. Our results are still to be replicated in other large cohorts.

Appendix 2 – Appendices relating to systematic review (chapter two)

2.1 Systematic review MESH headings

Search Strategy

Database search: Ovid Medline, Embase, and Cochrane Databases

Main Search

Epidemiology of Molluscum Contagiosum

[*"Molluscum Contagiosum"/ ep [Epidemiology]]

OR

[Molluscum Contagiosum, OR

Molluscum Contagiosum Virus

AND

Cross-sectional studies, OR

Prospective studies, OR

Incidence, OR

Prevalence, OR

Retrospective studies, OR

Population surveillance, OR

Questionnaires, OR

Case-control, OR

Risk Factors, OR

Health Surveys, OR

Disease outbreaks]

Appendix 3 – Appendices relating to MCDTP development and validation (chapters five and six)

3.1 Dermatologist questionnaire

REF: S1DSI [Phase 1: Dermatologist Structured Interview Schedule]
V 1.2 (12/10/2012)



Molluscum Contagiosum in the community **Dermatologist Structured Interview Schedule**

Inform Dermatologists of MOSAIC project, what their participation will involve and ask to complete Consent Form

Dermatologist Name _____

Date _____

Time _____

Location of Interview _____

Q1. Can you list the key diagnostic features of Molluscum Contagiosum?

Response

Q2. What are the features of Molluscum Contagiosum that a non-clinician (parent) would most easily recognise?

Response

Q3. Using the images of Molluscum Contagiosum provided, which would be most beneficial to use in a self-diagnostic aid? (select 3 to 4)

Do the images pick up the key diagnostic elements of Molluscum Contagiosum?

Are there any particular aspects of the photographs which should be zoomed on, annotated or highlighted?

Notes to be made on photographs, additional comments below

Response

Q4. Are there other skin conditions Molluscum Contagiosum may be confused with due to their similar appearance?

If yes, what characteristics of these conditions allow a differential diagnosis of MC?

Response

The information will be collated and used to produce a self-diagnostic 'MCDTP'.

Feedback from all dermatologists will be collated and circulated to Dermatologists.

Q5. Are you happy to receive and comment on this? Y ☐ N ☐

Thank participants for their time in taking part

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For office use only:
Participant ID:
D

3.2 Topic Guide

Key conversational topics for discussion with school and dermatology nurse, and patient representative

- 1) How would you describe a lesions/wart?
- 2) If you had a screening question to ensure of parents of children with lesions responded, what would you call the lesions?
- 3) Looking at the key wording below, how would you state this in a format non-clinicians could understand but still ensuring the key diagnostic criteria remain?

Firm, umbilicated pearly papules with a waxy surface

Firm papule lesions 1-5mm, umbilicated, folds,

Spots on the skin, flesh colours, domed shaped papules with central depression

- 4) Looking at the attached version of the parental diagnostic tool, is the instruction page and answer page clear?
- 5) In your opinion, what wording for a self-diagnostic tool would be best:

‘McTool’

‘Child Molluscum Contagiosum Diagnostic Tool (CMCDT)’

‘Molluscum Contagiosum Self Diagnostic Tool (MCSDT)’

‘Molluscum Contagiosum Diagnosing Aid (MCDA)’

‘Identifying Aid for Molluscum Contagiosum in Children (IAMCC)’

Or other....

3.3 MCDTP pilot questionnaire for parent group

REF: S1DPQ [Phase 1: Pilot with parents]
V 1.3 (13/08/2012)



Mollusum Contagiosum in the community

Contact: Mr Jonathan Olsen

'MCDTP' Parental Questionnaire

Please read the accompanying 'MCDTP' and answer the questions below in blue or black BLOCK CAPITALS or put a ☒ in the box.

Q1. Did you understand the instructions? Yes ☐ No ☐

Comments _____

Q2. Are you happy to complete this questionnaire on behalf of your child? Yes ☐ No ☐

Comments _____

Q3. What is your overall feedback of the 'MCDTP'?

Comments _____

Thank you for taking the time to complete the questionnaire.

Please return the questionnaire to the researcher.



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For office use only:
Participant ID:
DP

3.4 Molluscum contagiosum info sheet for GPs (Double-sided A4 document)

Molluscum Contagiosum Information sheet for GPs



As part of the MOSAIC study, we would like you to confirm whether or not some of your patients, who have used our self-diagnostic tool, actually have Molluscum Contagiosum (MC).

As a general practitioner, you will be familiar with diagnosing MC, and in most cases the diagnosis will be straightforward. However, occasionally it can be more difficult, and in order to try and ensure consistency in assessments, we have provided you with this 'aide-memoire', which has been prepared in collaboration with dermatologists at University Hospital Wales (UHW).



The key features of *Molluscum Contagiosum*

Lesions are typically discrete umbilicated pearly papules.

However, not all lesions have this distinctive central umbilication.

Lesions will be firm with a waxy smooth surface.

Flesh coloured and usually sized between 1 – 5 mm.





Lesions can be single or multiple.

Crops will normally appear in just one geographical area, typically a flexural site.

Children may also have Atopic Dermatitis in these sites during an episode of Molluscum Contagiosum.

Lesions are typically painless and will resolve within months, sometimes years.

There is often excoriation around lesions, and this can result in lesions appearing inflamed.



3.5 Letter of invitation to join MOSAIC study sent to practice managers

Department of Primary Care & Public Health
Head of Department Professor Christopher Butler
Adran Gofal Cynradd a Iechyd y Cyhoedd
Pennaeth Adran Yr Athro Christopher Butler



Molluscum Contagiosum in the Community

Thursday 15th November 2012

Dear Practice Manager,

I would like to invite you to participate in a researcher study being undertaken at Cardiff University about the common skin disease Molluscum Contagiosum.

For each participant you recruit into the study, your practice will receive a £35 payment. We hope you may recruit 20 patients or more.

Although Molluscum Contagiosum is a self-limiting skin virus in the UK, no previous study has described how many people in the community are affected with the virus. The impacts of disease, number of lesions, and how long these lesions last. **This is what our study aims to do.**

We hope the findings of the study will provide a clearer understanding of who Molluscum Contagiosum affects. This will ensure GPs and dermatologists are able to provide information to patients allowing them to have a more comprehensive understanding of this condition.

To do this we have designed a self-diagnostic Molluscum Contagiosum tool (MCDTP). This has been designed with the help of Dermatologists at University Hospital of Wales, Cardiff. We hope to use this to recruit a cohort of patients with Molluscum Contagiosum in the community and establish the prognosis and quality of life of patients with Molluscum Contagiosum in the UK.

However, we need to test the validity of our tool and this is where we **need your help**.

What this will involve for GPs

When a patient arrives at the GP consultation room with the "MCDTP", we ask that they clinically assess the lesion, noting on the form provided whether they would diagnose this as Molluscum Contagiosum or not.

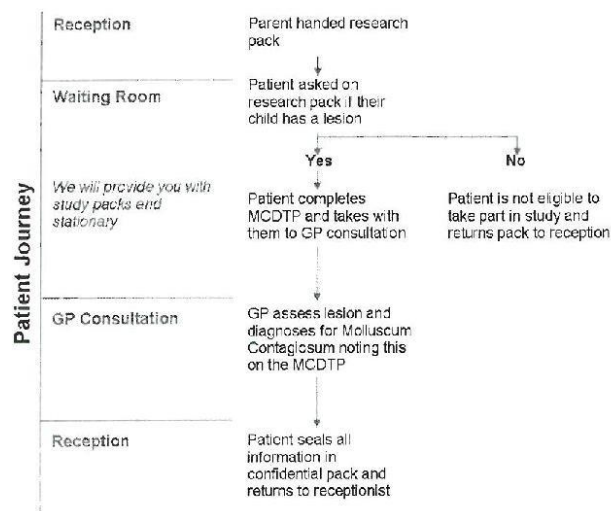


Department of Primary Care & Public Health
Cardiff University
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Neuadd Meirionnydd
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Fax/Facs +44(0)29 2068 7219
E-mail: E-bost geroract@cf.ac.uk

Adran Gofal Cynradd a Iechyd y Cyhoedd
Prifysgol Caerdydd
Grŵp Ymchwil Ffrygodisgyblaethol
Epidemiolog Glinigol
Yr Ysgol Faddysg
Neuadd Meirionnydd
Parc y Mynydd Dychan
Caerdydd CF14 4XN

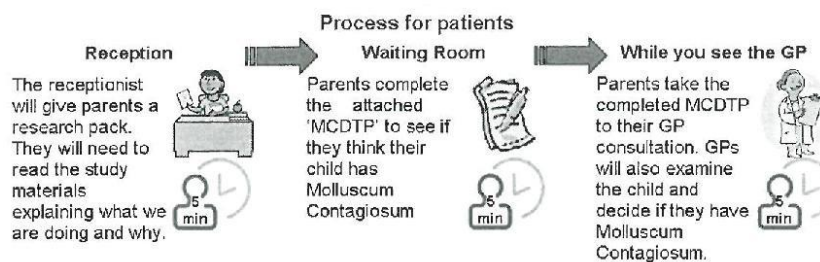


What this will involve for your practice?



Practice returns all completed forms to research team at Cardiff University in pre-paid envelope.

What this will involve for your patients



If you wish to take part:

The study will last for 6 months and we hope your practice recruits 50 patients or more.

If you wish to take part in the study, or have any questions, please contact myself, Jonathan Olsen on the details below.

Thank you for your time,



Mr Jonathan Olsen

Institute of Primary Care and Public Health, Cardiff University




Tel: (029) 20687157

Email: olsenjr@cardiff.ac.uk

3.6 MCDTP Validation - participant study pack

- a) Study envelope
- b) Participant information sheet
- c) Consent form
- d) MCDTP

a) Study envelope (printed size: A5)



We would like to invite you to participate in our study about diagnosing a common skin condition in children called Molluscum Contagiosum.

1. Does your child have a spot, lump or bump on their skin?
2. Is your child aged between 1 and 14 years?

If you answered yes to **both** these questions and would like to know more about the study and what it will involve for you and your child, please open the envelope.

****The study should take no longer than 5 minutes to complete while you wait to see the doctor****

If not, please return the pack to the receptionist.

Thank you for taking the time to read this.

b) Participant information sheet (A4 double-sided)

REF: S2PPP [Phase 2: Participant Information Sheet - GP Patients]
V 1.3 (13/08/2012)



Molluscum Contagiosum in the community – Information for Parents

Research Contact: Jonathan Olsen
Institute of Primary Care and Public Health, Cardiff University

We would like to invite you to take part in our research study. Before you decide whether you would like to take part, we would like you to understand why the research is being done and what it would involve for you.

Please take the time to read through the information sheet and contact us if it is unclear or you would like further information.

What is the purpose of the study?

We have designed a tool to help parents / guardians diagnose this skin condition in children. We need your help to see how well it works. The study is not testing to see how well you respond but the effectiveness of the tool we have designed.

Why have I been invited?

We are asking parents or guardians of children aged 1 to 14 to take part in our study.

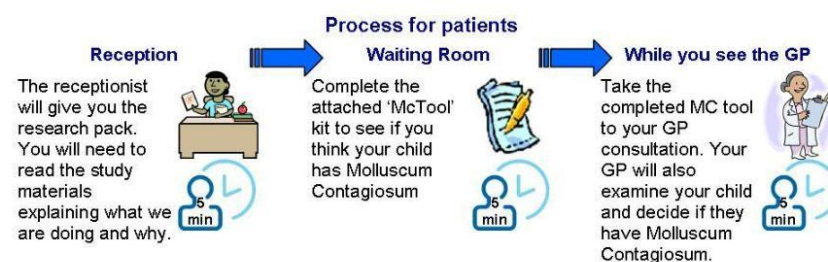
What is Molluscum Contagiosum?

Molluscum Contagiosum is a self-limiting skin condition which can affect any age but is more common in children. It usually presents with waxy dome shaped spots with a slight dip in the centre.

Do I have to take part?

No. Taking part in this study is voluntary, you are completely free to decline to participate without giving a reason and this will not affect the care you will receive during your child's consultation or future visits.

What happens if I decide to take part?



What happens next?

If you wish to take part in the study please complete the attached questionnaire whilst you wait to visit your GP. Not all children have Molluscum Contagiosum and this may be the case for your child. If you do not think that your child has Molluscum Contagiosum please still complete the questionnaire and give this to your GP during the consultation.

We also ask that you discuss this with your child and ensure they are aware of what will happen and consent to participating. If your child is aged 11 and over they will need to read a study information sheet for those aged 11 and over, then sign an assent form.

What are the disadvantages of taking part?

At the end of your child's consultation with your GP they will ask if your child has any spots or warts on their body, they will then examine these; this examination should not take more than a couple of minutes.

What are the possible benefits of taking part?

You and your child will not gain any benefit, but by taking part in the study you may help the diagnosis of Molluscum Contagiosum by parents in the future.

What if there is a problem?

We do not anticipate any problems. However, if you are unhappy with any element of the study please contact the research team (details below).

Will the information be kept confidential?

Yes, we will not ask for any personal information from you or your child other than age and gender. All study data will be kept confidential and securely for 15 years.

What will happen to the results of the study?

Results of the study will report on whether the self-diagnostic tool works. We will seek to submit these findings to scientific journals for publication, and may be presented at scientific meetings or conferences.

Has the study been approved?

The study has been approved and given a favourable decision by the NRES Committee South Central – Berkshire B Research Ethics Committee. This ensures the research is allowed to be conducted and follows ethical guidelines.

Who is organising and funding the study?

The study has been funded by the School of Medicine / Institute of Primary Care and Public Health at Cardiff University. The study forms part of the PhD thesis of Mr Jonathan Olsen, a postgraduate researcher in Cardiff University.

Contact Details and Research Team

Dr Nick Francis (Chief Investigator)

Mr Jonathan Olsen (Research Contact)
Institute of Primary Care and Public Health
School Of Medicine, Cardiff University
Neuadd Merionnydd, Heath Park
Cardiff
CF14 4YS
olsenjr@cardiff.ac.uk
029 2068 7157



c) Consent form (A4)

CONFIDENTIAL
REF: S2PPC [Phase 2: Consent Form]
V 1.1 (13/08/2012)

Molluscum Contagiosum in the community

Research Contact: Jonathan Olsen
Institute of Primary Care and Public Health, Cardiff University

If you are interested in taking part in this study and have had time to read the study information please complete this form and return to the researcher in the envelope provided.

Please provide your contact details below:

Childs Name _____

Full Name (Parent/Guardian) _____

Address _____

Postcode _____

Please initial
each box

I confirm that we have received the Participant Information leaflet (version 1.3 dated 13/08/2012) for the above study. We have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
We agree to participate in the above study	
We understand that our participation is voluntary and that we are free to withdraw at any time, without giving any reason.	
I agree that information we submit will be recorded. We understand that the information will be treated as confidential. I give permission for the anonymised data to be used in any research publications that result from the study.	
We understand that relevant sections of the data collected during the study may be looked at by individuals from Cardiff University, or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.	

Name (Parent / Guardian)

Date

Signature

Name (Child, if able to sign)

Date

Signature

Jonathan Olsen

Name (Researcher)

Date

Signature

For office use only:
Participant ID:
DP



Contact Details

Institute of Primary Care and Public Health
School Of Medicine, Cardiff University
Neuadd Merionnydd, Heath Park
Cardiff
CF14 4YS
olsenjr@cardiff.ac.uk
029 2068 7157

d) MCDTP (four page colour booklet, size: A5)

Molluscum Contagiosum Diagnostic Tool for Parents (MCDTP)



A Tool specially designed for you to be able to recognise
Molluscum Contagiosum

Key Information

- This aim of the study is not to test you. It is designed to assess how useful our tool is.
- If you have any queries please contact the research team (using the details provided) who are available to answer any questions
- You must meet the following criteria to participate in the study

Check list (please tick box ☒)

- ☐ You have read the patient information leaflet
- ☐ You and your child agree to participate and have completed the consent forms
- ☐ Your child is aged between 1 and 14 years
- ☐ Your child has a spot, lump or bump on their skin

Childs details

Age (years)

Today's Date / /

Gender ☐ Male ☐ Female

Instructions

Read this form and use
the images and text to
examine your child's
spot, lump or bump



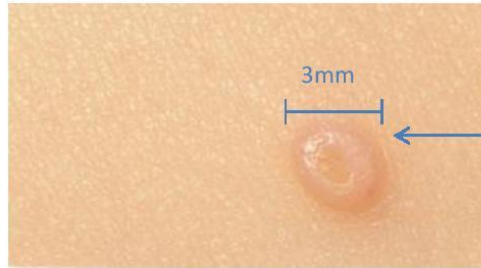
Complete the form
indicating whether you
think your child has
Molluscum Contagiosum



Once completed, take
this with you when you
see the Doctor



The key features of *Molluscum Contagiosum*



Small raised smooth spot on the skin.

Usually with a little dimple in the centre.

Usually the same colour as the skin.



Molluscum Contagiosum Diagnostic Tool for Parents (MCDTP)



A child can have just one spot, a few, or many.

Multiple spots will normally appear in just one area.

Most commonly on the tummy, back, arms, legs, or face.

The spots are usually painless.

In some children they can be itchy.

If the spots are scratched they may look red and sore.



Molluscum Contagiosum Diagnostic Tool for Parents (MCDTP)



Your diagnosis

1) Do you think your child has Molluscum Contagiosum? (please tick box ☒)

☐ Yes

☐ No

2) Using this scale, how confident are you with the answer you gave above?

Please **circle** your answer – example **Confident**

—	Very Confident
—	Confident
—	A bit confident
—	Not confident

Thank you for participating in the study.
Please take this form with you when you see the doctor

<u>For GP's only</u>	GP ID	<input type="text"/>	<input type="text"/>	<input type="text"/>
Name <input type="text"/>				
Diagnosis of MC	<input type="checkbox"/> Yes	<input type="checkbox"/> No		

Office use only

Practice ID	<input type="text"/>	<input type="text"/>	<input type="text"/>
Participant ID	<input type="text"/>	<input type="text"/>	<input type="text"/>

3.7 Medical photography protocol

Molluscum Contagiosum Photography Instructions








Equipment checklist:

- ✓ Camera
- ✓ Spare AA batteries x 4
- ✓ SD memory card in camera
- ✓ Measurement scales
- ✓ Photography instructions/camera settings
- ✓ Photography consent form
- ✓ Disposable background

Instructions for photography:

- Use a plain background where possible (preferably blue or green, ideally not white)
- Remove the lens cap before turning the camera on and pull up the flash
- Zoom as appropriate. Stand as far back as you can from the wound and use the zoom to fill the frame with the subject. If possible stand at least 1 metre away for an establishing photograph. Zoom in for a close-up, you may need to move a little closer
- The camera lens should be parallel to the plane of the wound except for the oblique photograph to show the lesion is raised
- Push the shutter release button halfway down to focus. When the camera is focused you will hear a beep and the focus square on the back of the camera will turn green. If the camera is not focused on the subject you will see an orange flashing square on the back of the camera. Release your finger from the shutter, you may need to physically move further back / forward or zoom the camera in / out. Make sure the camera is focusing on the lesion
- Take an establishing photograph to locate the lesion (see photographic guide)
- Take a close-up of the lesion using the scale.
- Check the image on the back of the camera
- Download images as soon as possible and delete the images off the camera

Setting the camera settings for the Olympus SP-620UZ camera:

Button		Function	Set to
Menu <i>button located bottom right on the back of the camera</i>		Image size	3M
		Compression	Fine
		Shadow adjust	Off
		AF Mode	Spot
		ESP	ESP
		Digital zoom	Off
		Image stabilizer	On
		AF illuminat.	On
		Rec view	On
		Pic orientation	On
		Icon guide	On
		Date stamp	Off
			Set date and time accurately
OK <i>Make sure you are not in 'Menu' mode</i>		Program	Set to 'P' Program Auto
		Flash	 Fill-in
		Macro	 Macro
		Timer	 Off
		Exposure comp.	0.0
		White balance	WB Auto
		ISO	400
		Number of frames	<input type="checkbox"/> Single

These views are intended as a guide however you may need additional photographs



Appendix 4 – Appendices relating to prospective cohort (chapter seven)

4.1 Molluscum contagiosum cohort questionnaire

Molluscum Contagiosum Questionnaire

Please complete all of the sections of the questionnaire.

Participant No.

--	--	--



Complete in **BLOCK CAPITALS** using blue or black ink, with either a ☐ or ☒ in the box.

Today's Date

D	D	/	M	M	/	Y	Y
---	---	---	---	---	---	---	---

Patient Information (Child with Molluscum Contagiosum)

Q.1 First name	<table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>																				
Q.2 Surname	<table border="1"><tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>																				
Q.3 Gender	<input type="checkbox"/> Male <input type="checkbox"/> Female																				
Q.4 Date of birth	<table border="1"><tr><td>D</td><td>D</td><td>/</td><td>M</td><td>M</td><td>/</td><td>Y</td><td>Y</td></tr></table>	D	D	/	M	M	/	Y	Y												
D	D	/	M	M	/	Y	Y														

About your child's Molluscum Contagiosum

Q.5 When did your child's Molluscum Contagiosum first appear?	<input type="checkbox"/> Less than 1 month <input type="checkbox"/> 1—2 months <input type="checkbox"/> 3—4 months <input type="checkbox"/> 5—6 months <input type="checkbox"/> 6—12 months <input type="checkbox"/> Over 12 months												
Q.6 How many Molluscum Contagiosum spots are currently present?	<input type="checkbox"/> 1 <input type="checkbox"/> 2—5 <input type="checkbox"/> 6—10 <input type="checkbox"/> 11—15 <input type="checkbox"/> 16—20 <input type="checkbox"/> 21+												
Q.7 Where are the Molluscum Contagiosum spots located? (tick all which apply)	<table><tr><td><input type="checkbox"/> Face</td><td><input type="checkbox"/> Arms (not hands)</td><td><input type="checkbox"/> Legs (not feet)</td></tr><tr><td><input type="checkbox"/> Neck</td><td><input type="checkbox"/> Hands</td><td><input type="checkbox"/> Feet</td></tr><tr><td><input type="checkbox"/> Back</td><td><input type="checkbox"/> Torso</td><td><input type="checkbox"/> Buttocks</td></tr><tr><td><input type="checkbox"/> Genitals</td><td><input type="checkbox"/> Armpits</td><td></td></tr></table>	<input type="checkbox"/> Face	<input type="checkbox"/> Arms (not hands)	<input type="checkbox"/> Legs (not feet)	<input type="checkbox"/> Neck	<input type="checkbox"/> Hands	<input type="checkbox"/> Feet	<input type="checkbox"/> Back	<input type="checkbox"/> Torso	<input type="checkbox"/> Buttocks	<input type="checkbox"/> Genitals	<input type="checkbox"/> Armpits	
<input type="checkbox"/> Face	<input type="checkbox"/> Arms (not hands)	<input type="checkbox"/> Legs (not feet)											
<input type="checkbox"/> Neck	<input type="checkbox"/> Hands	<input type="checkbox"/> Feet											
<input type="checkbox"/> Back	<input type="checkbox"/> Torso	<input type="checkbox"/> Buttocks											
<input type="checkbox"/> Genitals	<input type="checkbox"/> Armpits												

Please turn over for next page

Treatment	
Q.8	Has your child received treatment from a doctor for Molluscum Contagiosum? <input type="checkbox"/> Yes <input type="checkbox"/> No
	If Yes, what treatment
	<div></div>
Q.9	Have you treated your child's Molluscum Contagiosum with products/methods not prescribed by a doctor? <input type="checkbox"/> Yes <input type="checkbox"/> No
	If Yes, what treatment
	<div></div>
Q.10	Did you seek advice from anywhere else other than your Doctor about Molluscum Contagiosum? <input type="checkbox"/> Yes <input type="checkbox"/> No
	If Yes, where
	<div></div>
Q.11	Did your child have any other skin conditions in the months prior to Molluscum Contagiosum? <input type="checkbox"/> Yes <input type="checkbox"/> No
	If Yes, please list
	<div></div>
Activities and transmission	
Q.12	Does your child participate in any contact sports? <input type="checkbox"/> Yes <input type="checkbox"/> No
Q.13	Are there any other children aged 14 or under within the household? <input type="checkbox"/> Yes <input type="checkbox"/> No
	If yes, have any other members of the household recently also had Molluscum Contagiosum? <input type="checkbox"/> Yes <input type="checkbox"/> No

Please turn over for next page

Advice	
Q.14 Have you seen a doctor about your child's Molluscum Contagiosum at any point?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If Yes, did a doctor give you advice about the following:	
What Molluscum Contagiosum is?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Details _____	

How long the spots will last?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Details _____	

If the spots are contagious?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Details _____	

Should your child avoid physical contact with others?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Details _____	

Follow-up details	
<p>We would like to contact you by text or email each month until your child's spots have cleared. These texts will simply be to ask whether your child still has any spots, with a yes or no response.</p> <p>Please provide your preferred contact details below:</p> <p>Phone Number _____</p> <p>Email address _____</p> <p>Please also provide your address to enable us to post your £10 shopping voucher to thank you for your participation in the study</p> <p>Address line 1 _____</p> <p>Address line 2 _____</p> <p>County _____</p> <p>Postcode _____</p>	
Questionnaire Complete	

This is the last page

Page 3 of 3

4.2 Children's dermatology life quality index (CDLQI)

REF: SQOL [Phase 3: CDQLI (13/08/2012)]

The MOSAIC Study

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Participant Number:

CDLQI

Date:

SCORE:

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

- | | | | |
|-----|---|---|--|
| 1. | Over the last week, how itchy , "scratchy", sore or painful has your skin been? | Very much
Quite a lot
Only a little
Not at all | <input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/> |
| 2. | Over the last week, how embarrassed or self conscious , upset or sad have you been because of your skin? | Very much
Quite a lot
Only a little
Not at all | <input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/> |
| 3. | Over the last week, how much has your skin affected your friendships ? | Very much
Quite a lot
Only a little
Not at all | <input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/> |
| 4. | Over the last week, how much have you changed or worn different or special clothes/shoes because of your skin? | Very much
Quite a lot
Only a little
Not at all | <input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/> |
| 5. | Over the last week, how much has your skin trouble affected going out , playing , or doing hobbies ? | Very much
Quite a lot
Only a little
Not at all | <input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/> |
| 6. | Over the last week, how much have you avoided swimming or other sports because of your skin trouble? | Very much
Quite a lot
Only a little
Not at all | <input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/> |
| 7. | <div style="display: flex; align-items: center;"> <div style="margin-right: 10px;"> <u>Last week</u>,
was it
school time? </div> <div style="margin-right: 10px;"> </div> <div> If school time: Over the last week, how much did your skin problem affect your school work? </div> </div> <p style="text-align: center; margin: 5px 0;">OR</p> <div style="display: flex; align-items: center;"> <div style="margin-right: 10px;"> was it
holiday time? </div> <div style="margin-right: 10px;"> </div> <div> If holiday time: How much over the last week, has your skin problem interfered with your enjoyment of the holiday? </div> </div> | Prevented school
Very much
Quite a lot
Only a little
Not at all | <input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/> |
| 8. | Over the last week, how much trouble have you had because of your skin with other people calling you names , teasing , bullying , asking questions or avoiding you ? | Very much
Quite a lot
Only a little
Not at all | <input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/> |
| 9. | Over the last week, how much has your sleep been affected by your skin problem? | Very much
Quite a lot
Only a little
Not at all | <input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/> |
| 10. | Over the last week, how much of a problem has the treatment for your skin been? | Very much
Quite a lot
Only a little
Not at all | <input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/> |

Please check that you have answered EVERY question. Thank you.

©M.S. Lewis-Jones, A.Y. Finlay, May 1993, This must not be copied without the permission of the authors.

4.2 GP practice MOSAIC study information cards

[Phase 3: MOSAIC recruitment cards for General Practices]
V 1.3 (13/08/2012) [REF: S3PIL] (Page 1)



We would like to invite you to take part in a study about
Molluscum Contagiosum

What will it involve?

- Completing two short questionnaires (approx. 10mins)
- Email or text monthly follow up until condition clears (approx. 5mins each month until symptoms disappear)

The aims of the study are to understand more about how Molluscum Contagiosum presents in children, its effect on quality of life and how long it takes to recover..

As a token of thanks, we will give you £10 in high street vouchers.

[Phase 3: MOSAIC recruitment cards for General Practices]
V 1.3 (13/08/2012) [REF: S3PIL] (Page 2)

If you are interested in taking part or would like further information about the MOSAIC study please complete this reply slip and return it to the practice receptionist or go to <http://www.mosaic-study.co.uk/>.

☐ I would like to receive more information about the MOSAIC study

Name:

Telephone Number:

Email address:

Once complete please return this to the practice reception

<http://www.mosaic-study.co.uk/>

Institute of Primary Care and Public Health | School of Medicine | Cardiff University | Neuadd Merionnydd
Heath Park | Cardiff | CF14 4YS | olsenjr@cardiff.ac.uk | 029 2068 7157

4.4 Western Mail printed article about molluscum contagiosum and MOSAIC study

Western Mail [WesternMail.co.uk](#) Monday, 15 April 2013

HEALTH 23

fool you, now's the properly protected

levels of oil, helps keep the skin supple. Ointments have a higher oil content than creams and can therefore stay in the skin longer

privately high UV filter. And, remember, even on cloudy days UV light is filtering through the clouds, and can still cause damage.

Having suffered months of chilly weather as well as a wet summer, it's very tempting to

bake in the sunbather when we escape to warmer climes. But pale skin is very vulnerable to burning, so the usual precautions need to be taken.

Even if off-season Mediterranean sunshine is less powerful than during the baking

summer days, it is still strong. What's more, you don't need to be lying on the beach or in a sunbather, soaking up the rays on an outdoor terrace can still result in scorched skin.

Lately we must all remember to drink water. We may feel less

like having a glass of cool beer when the temperatures plain out, but keeping up our fluid intake is important.

Dr Harryono Jusohidharjo, founder and medical director of the Cellite Clinic, M18 BCh, MSc in Dermatology, PhD

Botox can make you miserable, says research

INJECTIONS of Botox to reduce 'crow's feet' can leave people feeling more depressed, according to new research.

A study carried out by Cardiff University psychiatrist Dr Richard Lewis on people who had received the treatment found that, depending on which facial lines were treated, discerned how depressed they felt.

The research, presented to the British Psychological Society's Annual Conference, found the treatment of frown

lines left the clients feeling less depressed, yet people who had received treatment for crow's feet reported feeling more depressed.

Dr Lewis said: "The expression that we make on our face affects the emotions we feel, and smiling also makes us happy."

Treatment with drugs like Botox prevents the patient from being able to make a particular expression.

For example, those treated

for frown lines with Botox are not able to frown as strongly. This interrupts the feedback they would normally get from their face and they feel less sad.

The new finding concerns the impact of treatments for crow's feet.

"The muscles around the eyes are used when forming a real smile and so it was predicted that treatment of the muscles that cause these will reduce the strength of a smile.

The results supported this prediction."

The effects of Botox on other emotions are also considered. Heightened feelings of disgust are a feature of some forms of Obsessive Compulsive Disorder (OCD). Dr Lewis proposes that drugs similar to Botox could be injected to reduce the facial expression of disgust. Such a treatment might reduce the patient's feelings of disgust and hence might reduce their OCD symptoms.

Diagnosing a child's skin problems can be tricky

Spots, lumps or bumps on your child's skin – could it be molluscum contagiosum? **Jonathan Olsen**, postgraduate researcher at the Institute of Primary Care and Public Health at Cardiff University, outlines the ongoing research into this common condition

■ Molluscum Contagiosum affects many children

SKIN conditions are more common than you might think, with up to 24% of the population visiting their GP about it.

Skin conditions can be irritating, physically affecting sleep and day-to-day activities, also impacting on quality of life. For children they can sometimes lead to name-calling, teasing and bullying.

Molluscum contagiosum, known generally as molluscum, is a common skin condition that affects people of all ages, but is seen mostly in children up to 14, especially in those under 10.

The name molluscum contagiosum refers to small skin-coloured spots suddenly appearing on the skin.

These viral spots are distinctive in appearance, having a small crater-like dip in the centre and appearing in a small localised crop, usually on the arms, back, tummy, or legs, which can last months or years. In some instances they can become troublesome, especially when accompanied by eczema, where the spots can be inflamed, itchy and sometimes get infected.

Sam, a parent of a young child with molluscum contagiosum, described the impact on her child, how she searched the internet to find out what her child's spots were, and what information she could find about molluscum contagiosum.

"The size of the spots caused skin irritation on his tummy, he was constantly scratching them through clothes and often made his skin raw" she said.

"Although it was easy enough to diagnose without the help of a doctor, finding out what to do was much more difficult. No website seemed to contain comprehensive information. My GP confirmed the diagnosis over the telephone but, even then, the advice about what to do was limited."

In the UK around 1% of children will get molluscum. There is a lot still unknown about the condition. This means when a

doctor diagnoses molluscum there is little information he or she can share with parents, such as how long the spots will last, will siblings develop spots, and does taking part in certain activities help the spots clear up.

At Cardiff University we want to find out more about molluscum and so we are recruiting as many children as we can to find out how the condition affects them and how long it lasts – this is what we aim to do.

We have developed an online tool which helps parents identify molluscum in their child. The molluscum contagiosum diagnostic tool for parents was designed with dermatologists at University Hospital of Wales, piloted with local parents, and tested in GP practices across Cardiff and Vale to ensure it is

works accurately. We have used the most effective images and text to support parents in making a diagnosis of molluscum.

We are inviting parents whose child either has been diagnosed with molluscum by a doctor, or they have spots, lumps or bumps on their skin, to take part in our study. When a parent signs up to the study they will be asked to complete two short online questionnaires, and then a monthly follow-up text or email until their child's spots have cleared.

The test simply asks whether molluscum is still present.

By logging onto [www.mosaic-study.co.uk](#), parents are able to view the tool, and use it to identify whether their child has molluscum.

The study is recruiting parents of children aged between four to 14 who have been diagnosed by a doctor, or they have a spot, lump or bump on their skin which they would like to diagnose using our parental diagnostic tool.

For more information visit the study website [www.mosaic-study.co.uk](#), and to keep up to date with information regarding the study follow us on twitter [@mosaic_study](#)

Spots, lumps or bumps on your child's skin....could it be Molluscum Contagiosum?

Skin conditions are more common than you might think with up to 24% of the population visiting their GP for a skin condition. Skin conditions can be are irritating; physically affecting sleep and day to day activities, also impacting upon quality of life. For children they can sometimes lead to name calling, teasing and bullying from other children.

Molluscum Contagiosum, known generally as Molluscum, is a common skin condition that affects people of all ages but is seen mostly in children aged 1 to 14, especially in those under 10. The name Molluscum Contagiosum may sound like a spell from Harry Potter, but it refers to small skin coloured spots suddenly appearing on the skin. These viral spots are distinctive in appearance, having a small crater like dip in the centre and appearing in a small localised crop, usually on the arms, back, tummy, or legs which can last months or years. In some instances they can become troublesome, especially when accompanied by eczema where the spots can be inflamed, itchy and sometimes get infected.

Sam, a parent of a young child with Molluscum Contagiosum, described the impact on her child, how she searched the internet to find out what her child's spots were, and what information she could find about Molluscum Contagiosum:

"The size of the spots caused skin irritation on his tummy; he was constantly scratching them through clothes and often made his skin raw....."

.....although it was easy enough to diagnose without the help of a doctor, finding out what to do was much more difficult. No website seemed to contain comprehensive information. My GP confirmed the diagnosis over the telephone but even then, the advice about what to do was limited."

In the UK around 1% of children will get Molluscum. There is a lot still unknown about Molluscum. This means when a doctor diagnoses Molluscum there is little information he or she can share with parents, such as how long the spots will last, will siblings develop spots, and does taking part in certain activities help or hinder the spots clearing-up. At Cardiff University, we want to find out more about Molluscum and so we are recruiting as many children as we can to find out how the condition affects them and how long it lasts – this is what we aim to do.

We have developed an online tool which helps parents identify Molluscum in their child. The Molluscum Contagiosum Diagnostic Tool for Parents (MCDTP) was designed with dermatologists at University Hospital of Wales, piloted with local parents, and tested in GP practices across Cardiff and Vale to ensure it works accurately. We have used the most effective images and text to support parents in making a diagnosis of Molluscum.

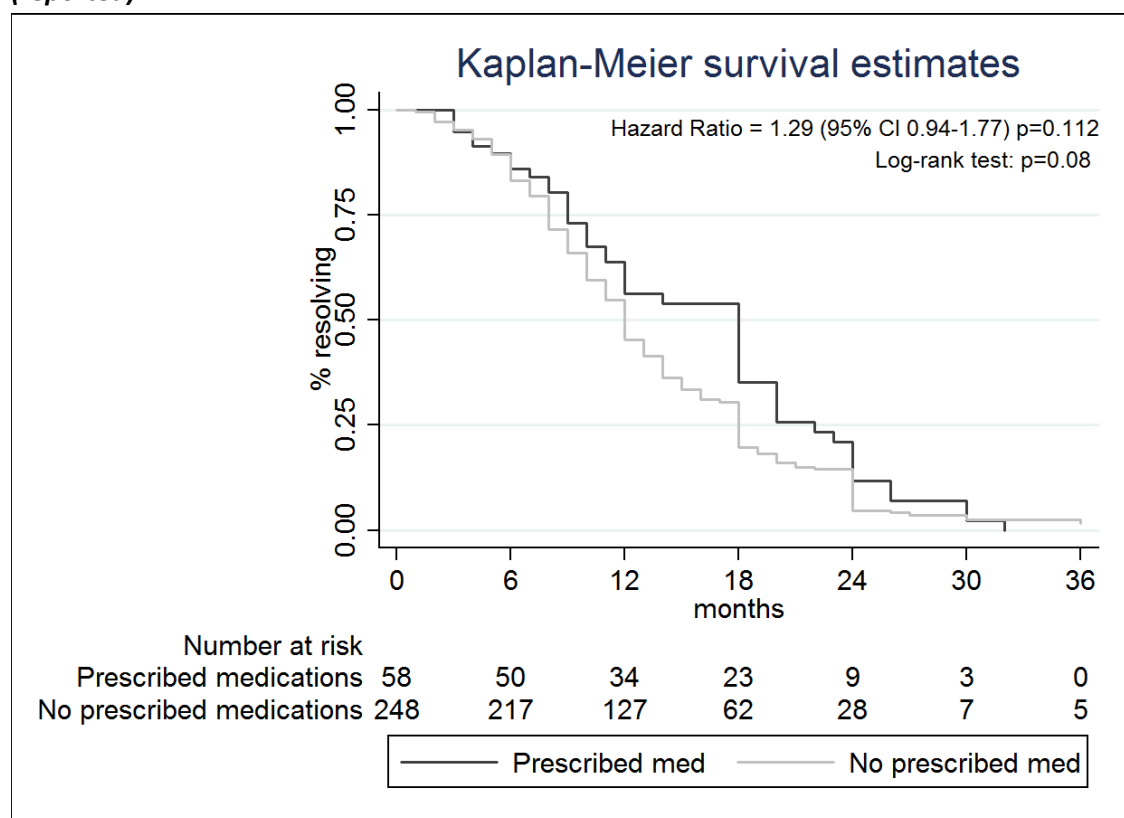
We are inviting parents whose child either has been diagnosed with Molluscum by a doctor, or they have spots, lumps or bumps on their skin, to take part in our study. When a parent signs up to the study they will be asked to complete two short online questionnaires, and then a monthly follow-up text or email until their child's spots have cleared. The text simply asks whether Molluscum is still present.

By logging onto www.mosaic-study.co.uk, parents are able to view the MCDTP, and using it, be able to identify whether their child has Molluscum.

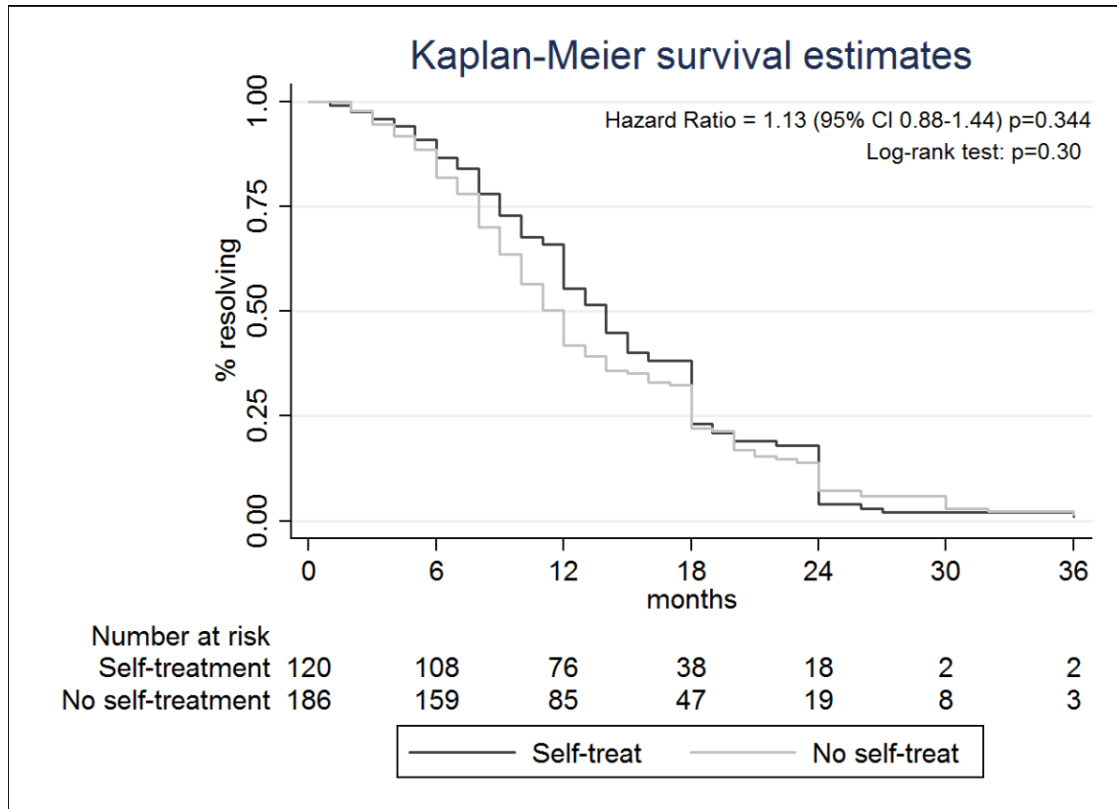
4.5 Kaplan-Meier survival estimates of MC lesions

- a) Kaplan-Meier survival estimates of lesions (in months) by prescribed medications (reported).
- b) Kaplan-Meier survival estimates of lesions (in months) by self-treatment (reported).
- c) Kaplan-Meier survival estimates of lesions (in months) by affected family member.
- d) Kaplan-Meier survival estimates of lesions (in months) by number of lesions (at baseline).

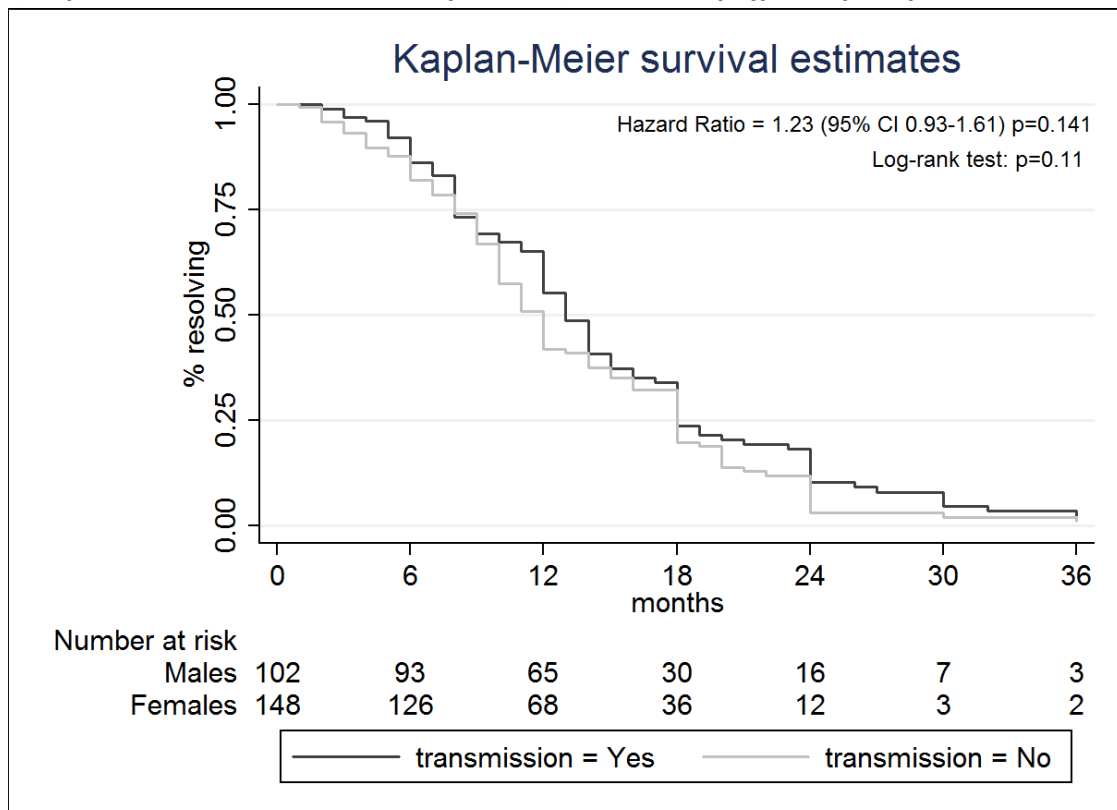
a) Kaplan-Meier survival estimates of lesions (in months) by prescribed medications (reported)



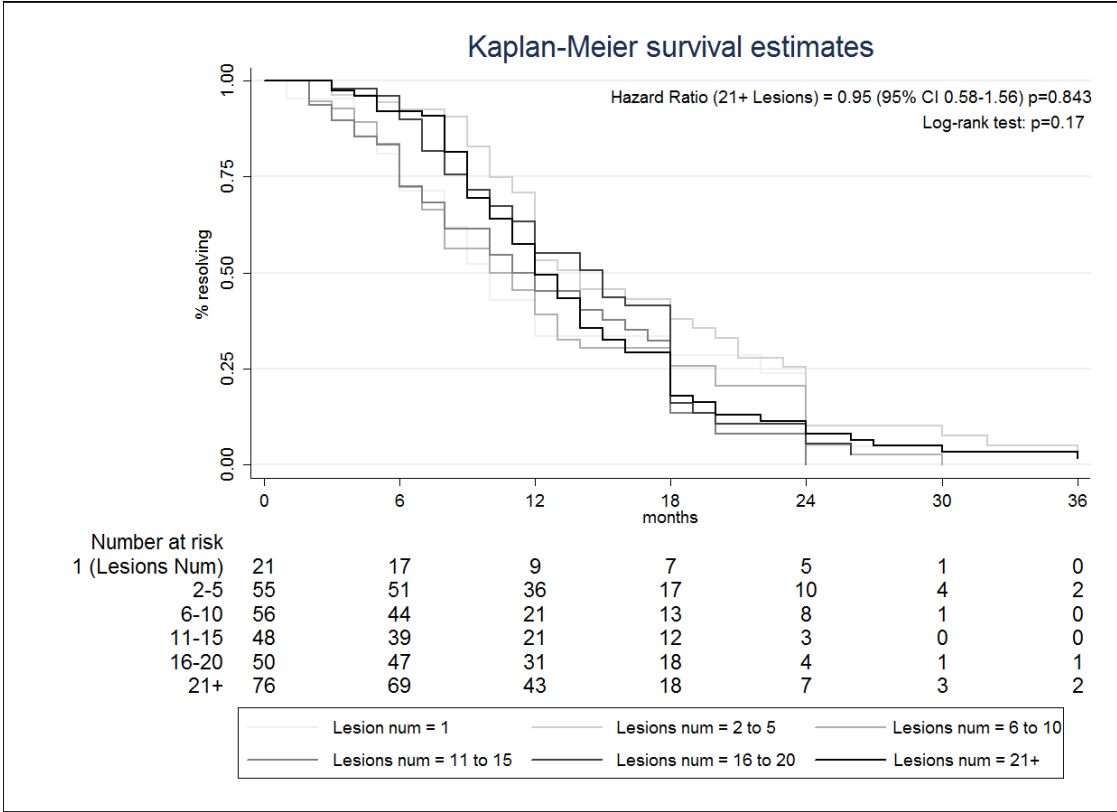
b) Kaplan-Meier survival estimates of lesions (in months) by self-treatment (reported)



c) Kaplan-Meier survival estimates of lesions (in months) by affected family member



d) Kaplan-Meier survival estimates of lesions (in months) by number of lesions (at baseline)



Appendix 5 – Ethical and research governance approval documentation

5.1 Research ethics committee (REC) approval



Health Research Authority

NRES Committee South Central - Berkshire B

Bristol REC Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 01173421335

Facsimile: 01173420445

21 August 2012

Dr Nick Francis
Senior Clinical Research Fellow
Cardiff University
Institute of Primary Care and Public Health
5th Floor, Neuadd Meirionnydd
Heath Park, Cardiff
CF14 4YS

Dear Dr Francis

Study title:	The MOSAIC Study: Molluscum Contagiosum in the Community: A description of the Epidemiology of the disease in the community.
REC reference:	12/SC/0455
IRAS project number:	100161
Protocol number:	SPON 1131-12

Thank you for your letter of 14 August 2012, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation.

Approved documents

The documents reviewed and approved by the Committee are:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Advertisement	1.1 Recruitment cards for GP	01 June 2012
Evidence of insurance or indemnity	Zurich	
Investigator CV		
Letter from Sponsor		13 July 2012
Other: Student CV		
Other: S3 'Signpost' card for patients	1.3	13 August 2012
Other: S3 CDQLI	1.1	13 August 2012
Participant Consent Form: S1 Dermatologist Consent Form	1.1	13 August 2012
Participant Consent Form: S1 Dermatology Parent Consent Form	1.1	13 August 2012
Participant Consent Form: S2 GP Patient Parent Consent Form	1.1	13 August 2012
Participant Consent Form: S2 Child Assent Form	1.1	13 August 2012
Participant Consent Form: S3 Parent consent Form	1.1	13 August 2012
Participant Consent Form: S3 Child Assent Form	1.1	13 August 2012
Participant Information Sheet: S1 Dermatologist Participant Information Sheet	1.2	13 August 2012
Participant Information Sheet: S1 Dermatology Parent Information Sheet	1.2	13 August 2012
Participant Information Sheet: S1 Dermatology Child Participant Information Sheet	1.1	13 August 2012
Participant Information Sheet: S2 Information Sheet for Practice Manager	1.2	13 August 2012
Participant Information Sheet: S2 Information Sheet for GP's	1.2	12 August 2012

Participant Information Sheet: S2 GP Patient Parent Participant Information Sheet	1.3	13 August 2012
Participant Information Sheet: S2 GP Child Participant Information Sheet	1.3	13 August 2012
Participant Information Sheet: S3 Information Sheet for General Practices	1.2	13 August 2012
Participant Information Sheet: S3 Information Sheet for General Practitioners	1.0	13 August 2012
Participant Information Sheet: S3 Patient Participant Information Sheet	1.2	13 August 2012
Participant Information Sheet: S3 Child Participant Information Sheet	1.1	13 August 2012
Protocol	1.8	14 August 2012
Questionnaire: Mollusum Contagiosum Questionnaire	1.2 Phase 3	12 June 2012
Questionnaire: McTool Parental Questionnaire	1.2 (Phase 1. Dermatology outpatients - Parents Q.)	19 May 2012
Questionnaire: S1 Dermatology Outpatient Questionnaire	1.3	13 August 2012
REC application	3.4	25 July 2012
Response to Request for Further Information		14 August 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/SC/0455	Please quote this number on all correspondence
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With the Committee's best wishes for the success of this project

Yours sincerely



Pp Dr Mike Arnott
Vice- Chair

Email: ubh-tr.berkshireB@nhs.net

Enclosures: *"After ethical review – guidance for researchers" [SL-AR2]*

Copy to: Miss Helen Falconer
falconerhe@cardiff.ac.uk

Cardiff And Vale University Health Board
research.development@cardiffandvale.wales.nhs.uk

Mr Olsen
olsenjr@cardiff.ac.uk

5.2 Research governance approval (Cardiff and Vale UHB)



GIG
CYMRU
NHS
WALES

Bwrdd Iechyd Prifysgol
Caerdydd a'r Fro
Cardiff and Vale
University Health Board

Eich cyf/Your ref
Ein cyf/Our ref
Welsh Health Telephone Network 1872
Direct line/Llinell uniongyrchol

Ysbyty Athrofaol Cymru
University Hospital of Wales

Heath Park,
Cardiff, CF14 4XW
Phone 029 2074 7747
Fax 029 2074 3838
Minicom 029 2074 3632

Parc Y Mynydd Bychan,
Caerdydd, CF14 4XW
Ffôn 029 2074 7747
Ffacs 029 2074 3838
Minicom 029 2074 3632

Tel: 029 20746986
Fax: 029 20745311
CAV_Research.Development@wales.nhs.uk

From: Professor JI Bisson
R&D Director
R&D Office, 2nd Floor TB2
University Hospital of Wales
Cardiff
CF14 4XW

14 November 2012

Professor Vincent Piguet
Department of Dermatology
3rd Floor Glamorgan House
Heath Park, Cardiff
CF14 4XN

Dear Professor Piguet

Cardiff and Vale UHB Ref : 12/CMC/5505 : Molluscum Contagiosum in the Community: A description of the Epidemiology of the disease in the community

NISCHR PCU Ref: 100161

The above project was forwarded to Cardiff and Vale University Health Board R&D Office by the NISCHR Permissions Coordinating Unit. A Governance Review has now been completed on the project.

Documents approved for use in this study are:

Document	Version	Date
NHS R&D Form	3.4	07/09/12
SSI Form	3.4	07/09/12
Protocol	1.9	22/10/12
Participant Information Sheet – Dermatologists Phase 1 (S1DRP)	1.2	13/08/12
Participant Information Sheet – Children Phase 1 (S1CPS)	1.1	13/08/12
Participant Information Sheet – Pilot Study with Parents Phase 1 (S1DPP)	1.3	22/10/12
Questionnaire Dermatology Outpatients – Parent – Phase 1 (S1DPQ)	1.3	13/08/12
Information for GPs – Phase 2 (S2GPP)	1.2	13/08/12
Information for Practice Managers – Phase 2 (S2PML)	1.2	13/08/12
Participant Information Sheet – Children Phase 2 (S2CPS)	1.3	13/08/12
Participant Information Sheet – Cohort Participants Phase 3 (S3PIS)	1.2	13/08/12

Page 1 of 2

Version 1.0. 09.06.10

Participant Information Sheet – Children Phase 3 (S3CIS)	1.1	13/08/12
Information for GPs – Phase 3 (S3GPL)	1.2	13/08/12
Recruitment card for GPs – Phase 3 (S3PIL)	1.3	13/08/12
Questionnaire Molluscum Contagiosum – Phase 3 (S3MCQ)	1.2	12/06/12
Questionnaire CDQLI – Phase 3 (SQOL)		13/08/12
Consent Form – Phase 2 (S2PPL)	1.1	13/08/12
Assent Form – Phase 2 (S2GCA)	1.1	13/08/12
Assent Form – Phase 3 (S3CAF)	1.1	13/08/12

I am pleased to inform you that the UHB has no objection to your proposal. This letter does not give you permission to begin this study.

You should now approach those primary care sites that you wish to include and invite them to participate. Please inform the R&D Office of which GP Practices wish to participate. An assessment will then be made by the UHB of the suitability of the Practices as a research site. Following a satisfactory assessment, Cardiff and Vale UHB will issue permission to undertake the study at that site.

You have informed us that Cardiff University is willing to act as Sponsor under the Research Governance Framework for Health and Social Care.

May I take this opportunity to wish you success with the project and remind you that as Principal Investigator you are required to:

- Inform the R&D Office if this project has not opened within 12 months of the date of this letter. Failure to do so may invalidate R&D approval.
- Inform NISCHR PCU and the UHB R&D Office if any external or additional funding is awarded for this project in the future
- Submit any substantial amendments relating to the study to NISCHR PCU in order that they can be reviewed and approved prior to implementation
- Ensure NISCHR PCU is notified of the study's closure
- Ensure that the study is conducted in accordance with all relevant policies, procedures and legislation
- Provide information on the project to the UHB R&D Office as requested from time to time, to include participant recruitment figures

Yours sincerely,



Professor Jonathan I Bisson
R&D Director

CC R&D Lead Prof Helen Houston
CC Sponsor contact Chris Shaw, RACD
CC Student Jonathan Olsen
CC Chief Investigator, Dr Nick Francis

5.3 Research study sponsorship

Research and Commercial Division
Director Geraint W Jones
Adran Ymchwil a Masnach
Cyfarwyddwr Geraint W Jones



13 July 2012

Dr Nick Francis
Institute of Primary Care and Public Health
School of Medicine
Cardiff University
5th Floor, Neuadd Meirionydd
Heath Park
Cardiff, CF14 4YS

Cardiff University
7th Floor
30 - 36 Newport Road
Cardiff CF24 0DE
Wales UK
Tel Ffôn +44(0)29 2087 5834
Fax Ffacs +44(0)29 2087 4189
Prifysgol Caerdydd
Llawr 7
30 - 36 Heol Casnewydd
Caerdydd CF24 0DE
Cymru Y Deyrnas Gyfunol

Dear Dr Francis,

Molluscum Contagiosum in the Community: A description of the Epidemiology of Molluscum Contagiosum in the Community.

I understand that you are acting as Academic Supervisor for the above PhD project to be conducted by Jonathan Olsen.

I confirm that Cardiff University agrees in principle to act as Sponsor for the above project, as required by the Research Governance Framework for Health and Social Care.

Scientific Review

I can also confirm that Scientific Review has been obtained from The Clinical Epidemiology IRG (School of Medicine).

Insurance

The necessary insurance provisions will be in place prior to the project commencement. Cardiff University is insured with Zurich Municipal. Copies of the insurance certificate are attached to this letter.

Approvals

On completion of your IRAS form (for NHS REC and NHS R&D approvals), you will be required to obtain signature from the Sponsor ('Declaration by the Sponsor Representative').

Please then submit the project to the following organisations for approval:

- the appropriate Research Ethics Committee(s);
- National Institute for Social Care Health Research Permissions Coordinating Unit (NISCHR PCU- to arrange host organisation R&D approval);

Once RACD has received evidence of the above approvals, the University is considered to have accepted Sponsorship and your project may commence.

Roles and Responsibilities

As Chief Investigator you have signed a Declaration with the Sponsor to confirm that you will adhere to the standard responsibilities as set out by the Research Governance Framework for Health and Social Care/ Medicines for Human Use (Clinical Trials) Regulations. In accordance with the University's Research Governance Framework, the Chief Investigator is also responsible for ensuring that each research team member is qualified and experienced to fulfill his/her delegated roles including ensuring adequate supervision, support and training.

The following contracts will be put in place prior to the research commencing:

- Site Agreement with General Practices involved.
- An appropriate confidentiality agreement with the student may also be necessary

May I take this opportunity to remind you that, as Chief Investigator, you are required to:

- ensure you are familiar with your responsibilities under the Research Governance Framework for Health and Social Care;

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Mae Prifysgol Caerdydd yn elusen gofrestredig, rhif 1136855



- undertake the study in accordance with Cardiff University's Research Governance Framework and the principles of Good Clinical Practice;
- ensure the Research complies with the Data Protection Act 1998;
- inform the Research and Commercial Division (RACD) of any amendments to the protocol or study design, including changes to start/end dates;
- co-operate with any audit inspection of the project files or any requests from RACD for further information.

You should quote the following unique reference number in any correspondence relating to sponsorship for the above project:

SPON 1131-12

This reference number should be quoted on all documentation associated with this project.

Yours sincerely



Dr K J Pittard Davies
Head of Research Policy & Management
Direct line: +44 (0) 29208 79274
Email: resgov@cardiff.ac.uk

Cc Jonathan Olsen

5.4 Independent scientific approval committee (ISAC)

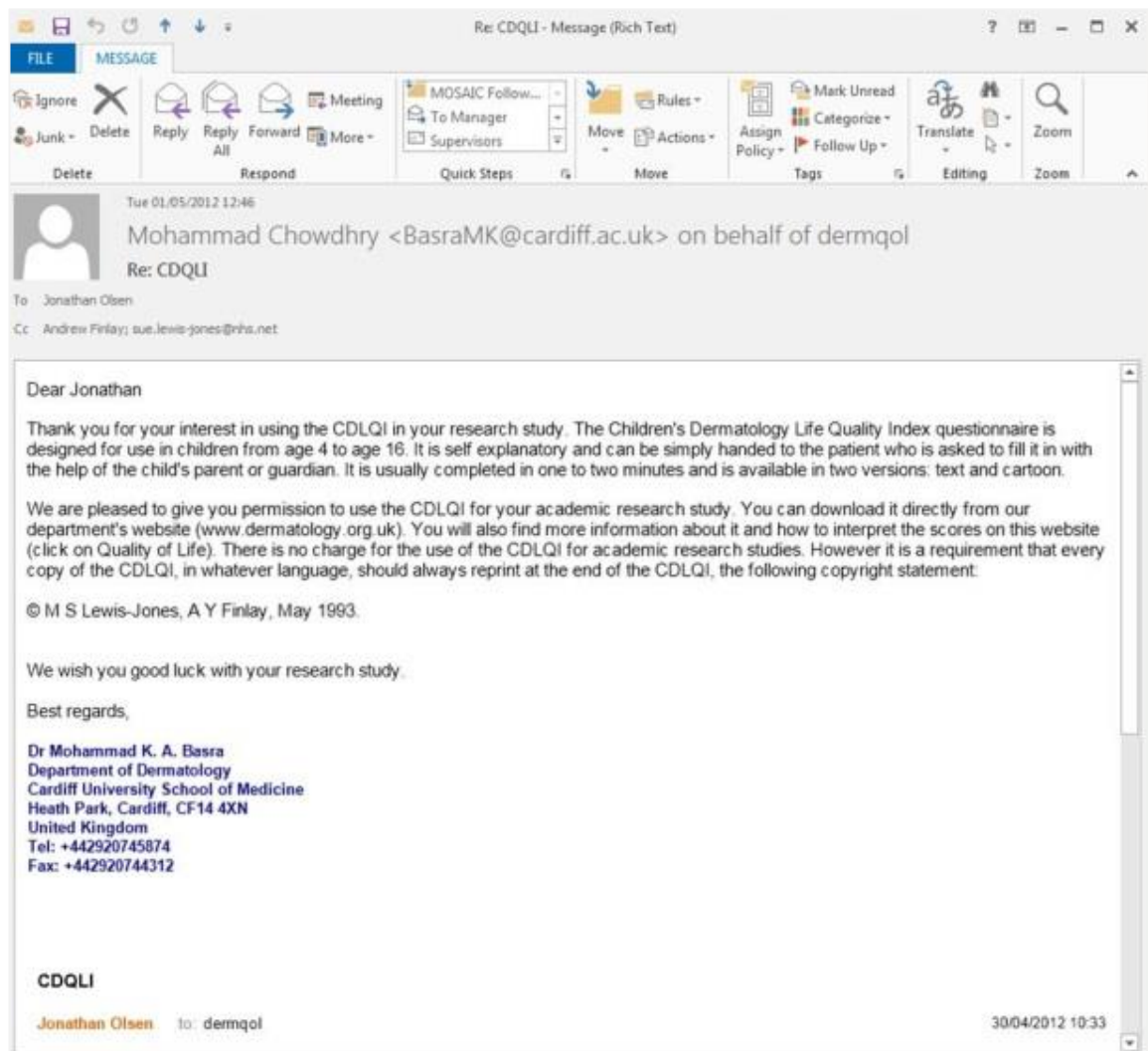
ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

FEED-BACK TO APPLICANTS

CONFIDENTIAL		by e-mail	
PROTOCOL NO:	14_058R		
PROTOCOL TITLE:	The Epidemiology of Mollusum Contagiosum: Incidence reporting to primary care in the UK		
APPLICANT:	Dr Nick Francis, Senior Clinical Research Fellow, Cardiff University		
APPROVED <input checked="" type="checkbox"/>	APPROVED WITH COMMENTS (resubmission not required) <input type="checkbox"/>	REVISION/ RESUBMISSION REQUESTED <input type="checkbox"/>	REJECTED <input type="checkbox"/>
INSTRUCTIONS: <i>Please include your response/s to the Reviewer's feedback below <u>only</u> if you are required to Revise/ Resubmit your protocol.</i> <i>Protocols with an outcome of 'Approved' or 'Approved subject to minor amendments' <u>do not</u> require resubmission to the ISAC</i> REVIEWER COMMENTS: Protocol 14_058R is approved.			
DATE OF ISAC FEEDBACK:		17 March 2014	
DATE OF APPLICANT FEEDBACK:			

**** Please refer to the ISAC advice about protocol amendments provided *below*****

5.5 CDLQI permission



5.6 WSPCR funding decision



Dr Nick Francis & Mr Jon Olsen
Cochrane Institute of Primary Care and Public Health
Cardiff University

15th October 2012

Dear Dr Francis and Mr Jon Olsen,

Re: Research Pilot Funding – Wales School for Primary Care Research

I am delighted to confirm that your application for research funding to support the pilot study "*The MOSAIC study. Molluscum Contagiosum in the Community: A description of the epidemiology of the disease in the community.*" was approved at the WSPCR Board on the 12th October 2012.

Your research funding will be for a total of **£15,890** made up of:

Cost to GPs per patient assesses (n=300) @ £35.00 each	£10,500
Participants contribution (n=300) @ £10.00 each	£3,000
Tablet computer for validating electronic version of 'McTool'	£390
Study website design to host 'McTool'.	£2,000

Please confirm the start and end dates for the study and a date for a mid project review. The WSPCR board will also require an end of study report to be submitted within 3 months of the project end date.

If you need any further support please do not hesitate contact me.

Best Regards,

A handwritten signature in black ink, appearing to read "Micaela Gal".

Micaela Gal

WSPCR Research Portfolio Development Fellow

Wales School for Primary Care Research, 5th Floor, Neuadd Meirionnydd, Heath Park, Cardiff
CF14 4XN

5.7 Letter of access for research (Cardiff and Vale UHB)



GIG
CYMRU
NHS
WALES

Bwrdd Iechyd Prifysgol
Caerdydd a'r Fro
Cardiff and Vale
University Health Board

Ysbyty Athrofaol Cymru
University Hospital of Wales

Heath Park,
Cardiff, CF14 4XW
Phone 029 2074 7747
Fax 029 2074 3838
Minicom 029 2074 3632

Parc Y Mynydd Bychan,
Caerdydd, CF14 4XW
Ffôn 029 2074 7747
Ffacs 029 20743838
Minicom 029 2074 3632

Eich cyf/Your ref
Ein cyf/Our ref
Welsh Health Telephone Network 1872
Direct Line/Ulinell uniongychol

30th November 2012

PRIVATE AND CONFIDENTIAL

Mr Jonathan Robin Olsen
83 A Crwys Road
Cardiff
CF24 4NF

Dear Mr Olsen

Letter of access for research

Title of Agreed Research Project: Molluscum Contagiosum in the Community:
A description of the Epidemiology of the disease in the community

Agreed Duties to be Undertaken: Pilot study with dermatologists and in
children's outpatient clinic

This letter confirms your right of access to conduct research through Cardiff and Vale UHB for the purpose and on the terms and conditions set out below. This right of access commences on 30th November 2012 and ends on 31st December 2012 unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at Cardiff and Vale UHB has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to Cardiff and Vale UHB premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through Cardiff and Vale UHB, you will remain accountable to your employer Cardiff University but you are required to follow the reasonable instructions of Professor A Anstey in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-

Letter of access for university researchers who do not require an honorary research contract
Version 2.1, September 2010

Page 1 of 3

operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with Cardiff and Vale UHB policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with Cardiff and Vale UHB in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on Cardiff and Vale UHB premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (<http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf>) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

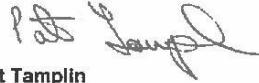
We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Where required by law, your HEI employer will initiate your Independent Safeguarding Authority (ISA) registration, and thereafter, will continue to monitor your ISA registration status via the on-line ISA service. Should you cease to be ISA-registered, this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity. You MUST stop undertaking any regulated activity.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

Cardiff and Vale UHB will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely



Pat Tamplin
Governance Officer HTA
Cardiff and Vale University Health Board

cc: **Employer's HR Department,**
NHS manager