Imiquimod for anogenital warts in non-immunocompromised adults (Review)

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Imiquimod para el tratamiento de verrugas anogenitales en adultos no inmunocomprometidos (Revisión Sistemática)

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To my beloved parents

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Abstract

Objectives: To assess the effectiveness and safety of imiquimod for the treatment of AGW in non-immunocompromised adults.

Methods: We searched the Cochrane STI Group Specialized Register, CENTRAL, MEDLINE, EMBASE, LILACS, among other sources. RCTs comparing the use of imiquimod with placebo, any other patient-applied or any other provider-administered treatment for the treatment of AGW in non-immunocompromised adults. Three review authors independently assessed trials for inclusion, extracted data and assessed risk of bias. We resolved any disagreements through consensus.

Results: Ten RCTs (1734 participants) met our inclusion criteria of which six were funded by industry. We judged the risk of bias of the included trials as high. Six trials compared the use of imiquimod versus placebo.

There was very low quality evidence that imiquimod was superior to placebo in achieving complete and partial regression (RR 4.03, 95% CI 2.03 to 7.99; RR 2.56, 95% CI 2.05 to 3.20, respectively) and frequency of systemic adverse reactions (RR 0.91, 95% CI 0.63 to 1.32) were imprecise.

Two trials compared the use of imiquimod versus any other patient-applied treatment (podophyllotoxin and podophyllin). The estimated effects of imiquimod on complete regression (RR 1.09, 95% CI 0.80 to 1.48), partial regression (RR 0.77, 95% CI 0.40 to 1.47), recurrence (RR 0.49, 95% CI 0.21 to 1.11) or the presence of local adverse reactions (RR 1.24, 95% CI 1.00 to 1.54) were imprecise (very low quality evidence).

Two trials compared imiquimod with any other provider-administered treatment (ablative methods and cryotherapy). There was very low quality of evidence that imiquimod did not have a lower frequency of complete regression (RR 0.84, 95% CI 0.56 to 1.28).

Conclusions: The benefits and harms of imiquimod compared with placebo should be regarded with caution due to the risk of bias, imprecision and inconsistency for many of the outcomes we assessed.

Keywords: Randomized controlled trials (RCTs), Anogenital warts (AGW), Sexually Transmitted Infections (STI), Review, Meta-Analysis, Imiquimod.

Resumen

Objetivos: Evaluar la eficacia y seguridad del imiquimod para el tratamiento de condiloma acuminado (AGW) en adultos no inmunocomprometidos.

Métodos: Se buscaron ensayos clínicos (RCTs) en el Registro Especializado del grupo Cochrane STI, CENTRAL, MEDLINE, EMBASE, LILACS, entre otros; que compararan el uso de imiquimod contra placebo, otro tratamiento aplicado por el paciente o administrado por el proveedor para el tratamiento de AGW en adultos no inmunocomprometidos. Tres autores evaluaron independientemente los estudios para incluir, extraer información y evaluar el riesgo de sesgo. El desacuerdo se resolvió por consenso.

Resultados: Diéz RCTs (1734 participantes) cumplieron criterios de inclusión, de los cuales seis fueron financiados por la industria. El riesgo de sesgo de los estudios se valoró como alto.

Seis estudios compararon imiquimod contra placebo. Hubo muy baja calidad de la evidencia sobre imiquimod superior a placebo; la estimación en regresión completa o parcial. (RR 4.03, 95% CI 2.03 a 7.99; RR 2.56, 95% CI 2.05 a 3.20, respectivamente) y reacciones adversas sistémicas (RR 0.91, 95% CI 0.63 a 1.32) fue imprecisa.

Dos ensayos compararon imiquimod contra otro tratamiento administrado por el paciente (podofilotoxina y podofilina). El efecto estimado de imiquimod en regresión completa (RR 1.09, 95% CI 0.80 a 1.48), regresión parcial (RR 0.77, 95% CI 0.40 a 1.47), recurrencia (RR 0.49, 95% CI 0.21 a 1.11) y reacción adversa local (RR 1.24, 95% CI 1.00 a 1.54) fue impreciso (muy baja calidad de la evidencia).

Dos ensayos compararon imiquimod contra otro tratamiento administrado por el proveedor (métodos ablativos y crioterapia). Hubo muy baja calidad de la evidencia, con imiquimod no hubo menos frecuencia de regresión completa (RR 0.84, 95% CI 0.56 a 1.28).

Conclusiones: La eficacia y seguridad del imiquimod comparado con placebo debería tomarse con precaución considerando el riesgo de sesgo, imprecisión e inconsistencia en la mayoría de los desenlaces evaluados.

Palabras clave: Ensayo clínico, condiloma acuminado, infección de transmisión sexual (STI), revisión, metanálisis, imiquimod.

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List of symbols and abbreviations

Symbol	Term	Unit IS	Definition
I^2	I-square	1	Percentage of total variation across studies that is due to heterogeneity rather than chance
p	p-value	1	p-value
T	Tau	1	Estimated standard deviation of underlying effects across studies
T^2	Tau-square	1	An estimate of the between-study variance in a random-effects meta-analysis
X^2	Chi-square	1	Cochran Q test
Z	z-statistic	1	Test for overall effect

Abbreviations

Abbreviation	Term
AGW	anogenital warts
B-TCA	bi- and trichloroacetic acid
BASHH	British Association for Sexual Health and HIV
DNA	deoxyribonucleic acid
CENTRAL	Cochrane Central Register of Controlled Trials
CRG	Cochrane Review Group
df	degrees of freedom
E(#)	early
EMBASE	Excerpta Medica database
FIGO	International Federation of Gynecology and Obstetrics
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HPV	human papillomavirus
ICAAC	Interscience Conference on Antimicrobial Agents and Chemotherapy
ICID	International Society for Infectious Diseases
ICTRP	WHO International Clinical Trials Registry
IMED	International Meeting on Emerging Diseases and Surveillance
INF	Interferon
ISSTDR	International Society for STD Research
IUSTI	International Union against STI
L(#)	late
LILACS	Literatura Latinoamericana y del Caribe en Ciencias de la Salud
MEDLINE	medical literature analysis and retrieval system online

Abbreviation	Term
M-H	Mantel-Haenszel
RRs	risk ratios
RCTs	randomized controlled trials
STI	sexually Transmitted Infections
TSC	trial search coordinator
5-FU	5 fluorouracil

Summary[1]

Background

30% of people with anogenital warts (AGW) have spontaneous regression of lesions but there is no way to determine whether a specific lesion will remain. There are a wide range of options available for treating people with AGW and selection is based on clinician's experience, patient preferences and adverse effects. The imiquimod could offer the advantages of patient-applied therapies without incurring the limitations of provider-administered treatments.

Objectives

To assess the effectiveness and safety of imiquimod for the treatment of AGW in non-immunocompromised adults.

Search methods

We searched the Cochrane Sexually Transmitted Infections Group Specialized Register (15 April 2014), CENTRAL (1991 to 15 April 2014), MEDLINE (1946 to 15 April 2014), EMBASE (1947 to 15 April 2014), LILACS (1982 to 15 April 2014), World Health Organization International Clinical Trials Registry (ICTRP) (15 April 2014), ClinicalTrials.gov (15 April 2014), Web of Science (2001 to 15 April 2014) and OpenGrey (15 April 2014). We also handsearched conference proceedings, contacted trial authors and reviewed the reference lists of retrieved studies.

Selection criteria

Randomized controlled trials (RCTs) comparing the use of imiquimod with placebo, any other patient-applied or any other provider-administered treatment (excluding interferon

[1] This document has been published elsewhere as form of the review entitled Imiquimod for anogenital warts in non-immunocompromised adults, published in The Cochrane Library 2014, Issue 11; available on: http://www.thecochranelibrary.com

and 5-fluorouracil which are assessed in other Cochrane Reviews) for the treatment of AGW in non-immunocompromised adults.

Data collection and analysis

Three review authors independently assessed trials for inclusion, extracted data and assessed risk of bias. We resolved any disagreements through consensus. The quality of the evidence was assessed using the GRADE approach.

Main results

Ten RCTs (1734 participants) met our inclusion criteria of which six were funded by industry. We judged the risk of bias of the included trials as high. Six trials (1294 participants) compared the use of imiquimod versus placebo. There was very low quality evidence that imiquimod was superior to placebo in achieving complete and partial regression (RR 4.03, 95% CI 2.03 to 7.99; RR 2.56, 95% CI 2.05 to 3.20, respectively). When compared with placebo, the effects of imiquimod on recurrence (RR 2.76, 95% CI 0.70 to 10.91), appearance of new warts (RR 0.76, 95% CI 0.58 to 1.00) and frequency of systemic adverse reactions (RR 0.91, 95% CI 0.63 to 1.32) were imprecise. We downgraded the quality of evidence to low or very low. There was low quality evidence that imiquimod led to more local adverse reactions (RR 1.73, 95% CI 1.18 to 2.53) and pain (RR 11.84, 95% CI 3.36 to 41.63).

Two trials (105 participants) compared the use of imiquimod versus any other patient-applied treatment (podophyllotoxin and podophyllin). The estimated effects of imiquimod on complete regression (RR 1.09, 95% CI 0.80 to 1.48), partial regression (RR 0.77, 95% CI 0.40 to 1.47), recurrence (RR 0.49, 95% CI 0.21 to 1.11) or the presence of local adverse reactions (RR 1.24, 95% CI 1.00 to 1.54) were imprecise (very low quality evidence). There was low quality evidence that systemic adverse reactions were less frequent with imiquimod (RR 0.30, 95% CI 0.09 to 0.98).

Finally, two trials (335 participants) compared imiquimod with any other provider-administered treatment (ablative methods and cryotherapy). There was very low quality of evidence that imiquimod did not have a lower frequency of complete regression (RR 0.84, 95% CI 0.56 to 1.28). There was very low quality evidence that imiquimod led to a lower rate of recurrence during six-month followup (RR 0.24, 95% CI 0.10 to 0.56) but this did not translate in to a lower recurrence from six to 12 months (RR 0.71, 95% CI 0.40 to 1.25; very low quality evidence). There was very low quality evidence that imiquimod was associated with less pain (RR 0.30, 95% CI 0.17 to 0.54) and fewer local reactions (RR 0.55, 95% CI 0.40 to 0.74).

Authors' conclusions

The benefits and harms of imiquimod compared with placebo should be regarded with caution due to the risk of bias, imprecision and inconsistency for many of the outcomes we assessed in this Cochrane Review. The evidence for many of the outcomes that show imiquimod and patient-applied treatment (podophyllotoxin or podophyllin) confer similar benefits but fewer systematic reactions with the Imiquimod, is of low or very low quality. The quality of evidence for the outcomes assessing imiquimod and other provider-administered treatment were of very low quality.

1. Background[2]

1.1 Description of the condition

Description of the condition Human papillomavirus (HPV) is an non-enveloped, doublestranded DNA virus with an eight kilobase pair-long genome, which is comprised of eight open reading frames that encode early and late genes involved in the expression of non-structural (early: E1, E2, E5, E6 and E7) and structural (late: L1 and L2) proteins during the viral life cycle. HPVs are classified as “types” based on their genetic similarities (Grillo-Ardila 2008). Currently, 180 different HPV types have been classified, approximately 30 of which have been found to infect genital epithelia. They are named “oncogenic” or “high risk” when they are associated with genital organ cancers (e.g. HPV 16, 18, 31 to 37). The other types are named “non-oncogenic” or “lowrisk” and are associated with genital warts (HPV 6 and 11) (Wiley 2002).

HPV specifically infects and replicates in the lower levels of the stratified epithelium. The spectrum of the infection includes the acquisition of the virus without pathological changes at the cellular level to intraepithelial neoplasia (Mayeaux 2008). Dysplastic changes begin with minor cytological changes, such as koilocytes and warts, to malignant changes. The natural history of diseasegoes from spontaneous clearance of the virus, a few months after acquisition in some cases, to the development of carcinoma of the genital tract in other cases (Wiley 2002). Regarding genital warts,no studies specifically show the time and the percentage of virus clearance from lesions (Wiley 2002).

Up to 75%of sexually-active adults have been exposed to the HPV virus (as detected by HPV antibodies) and around 15% to 20% of them carry the virus (detected as HPV DNA by polymerase chain reaction) (Garland 2002). An estimated 1% of sexually active adults have

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[2] This document has been published elsewhere as form of the review entitled Imiquimod for anogenital warts in non-immunocompromised adults, published in The Cochrane Library 2014, Issue 11; available on: http://www.thecochranelibrary.com

genital warts (Weinstock 2004). The incidence of genital HPV infections decreases with age. Thus, detection of HPV infection among older women is more likely to reflect persistent infection, whereas detection among younger women more often represents recently acquired and probably transient infection (Ho 1998).

Anogenital warts (AGW) occur on the penis, scrotum, vagina, vulva, anus and perineal areas and inguinal folds; areas that are traumatized during intercourse. Condylomas may be solitary but generally comprise from five to more than 15 lesions of 1 mm to 10 mm diameter. Warts may coalesce into large plaques (von Krogh 2000). The warts can be macular or flat, keratotic, pedunculated, and acuminate or cauliflower-shaped. Symptoms may include inflammation, pain, fissuring, itching, bleeding or dyspareunia (von Krogh 2000). Diagnoses of AGW are primarily clinical (Garland 2002) by visual examination supported by a magnifying glass if necessary; this is the only recommended test for diagnosis and cure evaluation (Maw 2000). The acetic acid test is not a specific test for HPV infection and it should not be used for screening; nor is a biopsy, with or without viral typing, recommended for patients with typical lesions (Kodner 2004; Mayeaux 2008) because it doesn't modify the treatment of the condition (von Krogh 2000).

The differential diagnosis includes pearly penile papules and vulvars papillomatosis (normal variants), condyloma latum, seborrheic keratoses, dysplastic and benign nevi, molluscum contagiosum and neoplasms (Mayeaux 2008).

1.2 Description of the intervention

Although 30%of AGWspontaneously regress without treatment, there is no way to determine whether a specific lesion will regress, remain unchanged or increase in size (Berman 2012). Treatment should be offered to all patients with AGW (Workowski 2010).

There are several treatments available for the management of genital warts. The treatment aims to reduce symptoms and visible lesions, but doesn't eliminate HPV infection directly. Therapies such as interferon (IFN) and imiquimod treat the infection by stimulating immune responses (Dockrell 2001); the catechins has been involved in the regression of genital warts through the cell cycle arrest, apoptosis induction and the inhibition of HPV gene expression (Stockfleth 2012). In addition, cidofovir, an acyclic nucleoside phosphonate, directly affects viral replication and has been tested for treatment of HPV lesions (Ho 1998).

Treatment should be guided by the morphology, size, number and localization of the wart (Kodner 2004). Treatments are divided into provider and patient-applied therapy groups. Also, there are surgical and medical managements. Surgical treatments include electrosurgery, surgical excision, cryotherapy and laser surgery. Nonsurgical therapies, such as podophyllin, IFN and bi- and trichloroacetic acid (BCA, TCA) can be provider-applied. Patientapplied medications include podophyllotoxin, imiquimod, catechins and 5-fluorouracil (5-FU) cream (Ho 1998; Workowski 2010). Imiquimod is indicated for the treatment of external AGW, superficial basal cell carcinoma and actinic keratoses (Wagstaff 2007). It has the potential to treat other HPV-associated conditions such as flat warts, plantar warts and common warts (Verruca vulgaris) (Marini 2002).

Imiquimod is used topically in cream form, with concentrations from 1% to 5%, by application daily or three times per week for eight to 16 weeks. Patients must be advised to wash the affected area with soap and water six to 10 hours after the application (Garland 2002; Weinstock 2004). Systemic absorption is minimal (Miller 1999b). The drug is retained in the skin for prolonged periods, resulting in an elimination half-life of one day. Imiquimod and its active metabolites (S26704 and S27700) are excreted in urine and faeces (Wagstaff 2007).

Application of imiquimod can produce local skin reactions; the most frequent ones are local pruritus, erythema, excoriation or flaking, erosion, edema, and scabbing or crusting. Systemic adverse events are rare and include headache, fatigue, myalgia and nausea. Other adverse events are decreases in hemoglobin, white blood cells and platelets. Reactions have been reported in skin at distant sites, such as erythema multiform, Steven Johnson syndrome and cutaneous lupus erythematosus (Wagstaff 2007).

1.3 How the intervention might work

Imiquimod is a novel synthetic imidazoquinoline (1-[2-methylpropyl]-1H-imidazo[4,5-c]quinolin-4-amine) (Marini 2002). HPV is non-cytolytic, has no systemic phase and its replication is not accompanied by inflammation (Garland 2002) with the consequent evasion of antigen presentation, delaying the immune system activation. The clinical efficacy of topical imiquimod is secondary to the stimulation of both innate and cell-mediated immune responses to tumour and viral antigens (Dockrell 2001). The monocytes, keratinocytes, Langerhan’s cells and T-lymphocytes are stimulated to produce cytokines (INF-α and IL 1, 6, 8, 10 and 12); also B-lymphocytes proliferate to produce

immunoglobulins (Dockrell 2001). This drug produce inhibition of associated pathological angiogenesis via stimulated apoptosis (Buck 1998; Schön 2007).

1.4 Why it is important to do this review

Currently, there are a wide range of therapies available for people with AGW (Workowski 2010). Choice is based on the experience of the healthcare provider, patient preference, cost of treatment, adverse effects and the feasibility of a given procedure (Maw2004), in addition to the absence of definitive evidence which shows which therapy is superior (Workowski 2010).

Traditionally, patient-applied treatment, such as podofilox and catechins (green tea), is frequently associated with local reactions like irritation, induration, erosion, pruritus, pain and edema. Provideradministered treatments (BCA, TCA, cryotherapy and surgical removal) require substantial clinical training, additional equipment, local or general anesthesia and longer office visits with some risk of systemic absorption and toxicity (Workowski 2010), all of which limit applicability in clinical practice.

In the USA and Europe, imiquimod is indicated for treatment of people with external genital and perianal warts and its efficacy in immunocompetent patients has been assessed in several studies. Complete clearance of the warts occurred in 40% to 70% of imiquimod recipients after application three-times weekly or daily for eight to 16 weeks. Imiquimod has also been used in superficial basal cell carcinoma, demonstrating superiority to placebo, with complete resolution of lesions in 79% to 87% of patients (Wagstaff 2007).

Currently, there are no systematic reviews comparing the effectiveness and safety of imiquimod with other available therapies for treating AGW in non-immunocompromised adults. Imiquimod could offer the advantages of patient-applied therapies with a low local reaction rate, without incurring the limitations of provider-administered treatments. Thus it is necessary to assess the effectiveness and safety of imiquimod for treating AGW in non-immunocompromised adults. Interferon (Chen 2009) and 5-FU (Batista 2010) are also considered treatments for AGW but are assessed separately in other Cochrane Reviews.

2. Methods[3]

2.1 Criteria for considering studies for this review

2.1.1 Types of studies

Randomized controlled clinical trials, published and unpublished, comparing imiquimod as first-line therapy with placebo, expectant management, any other patient-applied treatment or any other provider-administered therapy for the treatment of AGWin nonimmunocompromised adults. We excluded quasi-randomized trials because this produce effects estimates that indicate more extreme benefits when they are compared with randomized clinical trials (Higgins 2011). Also we excluded cross-over trials because the carry over effect (Higgins 2011).

2.1.2 Types of participants

Men and non-pregnant women with immunocompetence, aged over 16 years and clinically diagnosed with AGW regardless of biopsy confirmation. We excluded participants that did not have clinically visible lesions.

2.1.3 Types of interventions

Imiquimod treatment (of any concentration, frequency and dura-tion) versus:

- placebo;
- expectant management;
- any other patient-applied treatment such as podofilox or catechins (any concentration, frequency and duration of treatment); or

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[3] This document has been published elsewhere as form of the review entitled Imiquimod for anogenital warts in non-immunocompromised adults, published in The Cochrane Library 2014, Issue 11; available on: http://www.thecochranelibrary.com

- any other provider-administered treatment such as TCA, BCA, cryotherapy or surgical removal (any concentration, frequency and duration of treatment).

We excluded interferon (Chen 2009) and 5-FU (Batista 2010) treatment as these have been assessed in other Cochrane Reviews.

2.1.4 Types of outcome measures

Primary outcomes

1. Complete regression after treatment (total clearance of the warts).

2. Partial regression after treatment (at least 50% clearance of he lesions).

3. Dyspareunia after treatment.

Secondary outcomes

1. Time to complete regression.
2. Relief of symptoms during treatment.
3. Recurrence during follow-up (from 0 to six months, and from six to 12 months)
4. Appearance of new warts during treatment.
5. Excessive scarring at application site (hypertrophic scar or keloid).
6. Time to resumption of intercourse.
7. Pain during therapy.
8. Pigmentary changes at application site (hypo- or hyperpigmentation at the site of application).
9. Any local adverse reactions during therapy (erythema, irritation, ulceration, erosion, edema, flaking or induration).
10. Any systemic adverse reactions during therapy (headache, fatigue, myalgia, nausea, decrease of hemoglobin or white blood cells or platelets, erythema multiform, Steven Johnson syndrome or cutaneous lupus erythematosus).
11. Requirement of any additional patient-applied or provider-administered treatment at the end of the therapy.
12. Patient's satisfaction with treatment.
13. Cost effectiveness of imiquimod.

2.2 Search methods for identification of studies

We attempted to identify as many relevant randomized controlled trials (RCTs) as possible of “imiquimod” for “anogenital warts”, irrespective of language of publication, publication date and publication status (published, unpublished, in press and in progress). We used both electronic searching in bibliographic databases and handsearching, as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

2.2.1 Electronic searches

We contacted the Trials Search Coordinator (TSC) of the Cochrane Sexually Transmitted Infections Group in order to implement a comprehensive search strategy to identify as many relevant RCTs as possible in electronic databases. We used a combination of controlled vocabulary (MeSH, Emtree, DeCS, including exploded terms) and free-text terms (considering spelling variants, synonyms, acronyms and truncation) for “anogenital warts” and “imiquimod”, with field labels, proximity operators and Boolean operators. We have listed our search strategies in Appendix 1.

We searched the following electronic databases:

- Cochrane Sexually Transmitted Infections Group Specialized Register (15 April 2014).
- Cochrane Central Register of Controlled Trials (CENTRAL), Ovid platform (1991 to 15 April 2014).
- MEDLINE, Ovid platform (1946 to 15 April 2014).
- MEDLINE In-Process & Other Non-Indexed Citations, Ovid platform (1946 to 15 April 2014).
- MEDLINE Daily Update, Ovid platform (1946 to 15 April 2014).
- EMBASE (1947 to 15 April 2014).
- LILACS, IAHx interface (1982 to 15 April 2014).

For MEDLINE, we used the Cochrane highly sensitive search strategy for identifying RCTs: sensitivity and precision maximizing version (2008 revision), Ovid format (Higgins 2011). We combined the LILACS search strategy with a RCTs filter of IAHx interface.

2.2.2 Searching other resources

We searched the following resources for additional trials:

1. Trial registers:
   - WHO International Clinical Trials Registry Platform ICTRP portal (http://apps.who.int/trialsearch/).
   - ClinicalTrials.gov (http://clinicaltrials.gov/).

2. Web of Science® (2001 to 15 April 2014).

3. System for Information on Grey Literature in Europe "OpenGrey" (http://www.opengrey.eu/): 1990, 1992, 1995, 1996 and 1997.

4. We contacted the trial authors of all RCTs we identified by other methods.

5. We contacted pharmaceutical companies producing imiquimod for AGW.

6. We handsearched the following journals: Anatolian Journal of Obstetrics & Gynecology, Current Medical Literature Gynecology & Obstetrics, Current Obstetrics and Gynecology Reports, ISRN Obstetrics and Gynecology, Journal of South Asian Federation of Obstetrics & Gynecology, Obstetrics and Gynecology International, Obstetrics Gynaecology and Reproductive Medicine, and Sexual Science: the Newsletter of the Society for the Scientific Study of Sexuality and Sexualities.

7. Also we handsearched conference proceeding abstracts of the following events:
   - The International Society for Sexually Transmitted Diseases Research (ISSTDR) (http://www.isstdr.org/): 2007, 2009 and 2011.
   - The British Association for Sexual Health and HIV (BASHH) (http://www.bashh.org/): 2004, 2006, 2007 and 2009.
   - International Congress on Infectious Diseases (ICID) (http://www.isid.org/): 2010 and 2012.
   - The International Union against Sexually Transmitted infections (IUSTI) (http://www.iusti.org/): 2011 and 2012.
   - International Society for Infectious Diseases (ISID) (http://www.isid.org/): 2011.
   - International Meeting on Emerging Diseases and Surveillance (IMED) (http://www.isid.org/): 2007, 2009 and 2011.
   - Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) (http://www.icaac.org/): 2011 and 2012.

- The International Federation of Gynecology and Obstetrics (FIGO) (http://www.figo2012.org/ home/): 2012.

8. We handsearched within previous systematic reviews, within other relevant ublications on the same topic and the reference lists of all RCTs identified by other methods.

2.3 Data collection and analysis

2.3.1 Selection of studies

Three review authors (CFGA, EAM and LCSD) independently assessed for inclusion all the titles and abstracts of records retrieved from the search strategy. The final selection of trials for inclusion was undertaken independently by three review authors and we resolved any disagreements through discussion.

2.3.2 Data extraction and management

We designed a data extraction form which was pilot tested. Three review authors (CFGA, EAM and LCSD) independently extracted from the eligible trials. We discussed any disagreements regarding extracted data until we reached consensus.

We extracted information on the following items:

- Location of the trial and setting.
- Trial design.
- Power calculation performed.
- Inclusion and exclusion criteria.
- Baseline information of the participants in order to have comparable intervention groups at entry (number of women, number of men, site, size, number and shape of lesions, number of participants who received imiquimod as first-line therapy or as second-line therapy).
- Total number of intervention groups.
- Types of interventions: imiquimod any concentration, frequency and duration of treatment.
- Types of comparison: any patient-applied treatment (any concentration, frequency and duration of treatment) or any other provider-administered treatment (any concentration, frequency and duration of treatment).

- Number of subjects enrolled, randomized, excluded after randomization and analyzed.
- Number of participants lost to follow-up in the groups.
- Outcomes stated in methods versus outcomes reported in results.
- How secondary outcomes were defined.
- Differences between groups for outcome assessment.
- Time of follow-up of participants for specific outcomes.
- How adverse event reports were validated.
- Funding sources reported.
- Ethical issues: use of signed informed consent and ethics approval.

We entered data into Review Manager (RevMan) and checked them for ensuring data quality. When information regarding any of the above was unclear, we contacted authors of the original reports for further details. For a single randomized controlled clinical trial report, we extracted data directly onto the data extraction form. In the case of multiple reports, we extracted data from each report separately and then combined them across the forms.

2.3.3 Assessment of risk of bias in included studies

Three review authors (CFGA, LCSD and EAM) independently assessed risk of bias for each included trial using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We resolved any disagreements by consensus or by involving a third review author (HGD). The review authors that assessed risk of bias were thematic and methodology experts. We assessed the following information which we used to complete the risk of bias tables.

Random sequence generation (checking for possible selection bias)

For each included trial we recorded the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We assessed the method as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or unclear risk of bias.

Allocation concealment (checking for possible selection bias)

We determined the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen before or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes); high risk of bias (e.g. open random allocation; unsealed or non-opaque envelopes; alternation; assignment by date of birth); or unclear risk of bias.

- **Blinding of participants and personnel (checking for possible performance bias)**

We described for each included trial the methods used, if any, to blind trial participants and personnel from knowledge of which intervention a participant received. We considered that trials were at low risk of bias if no blinding or incomplete blinding, but we judged that the outcome is not likely to be influenced by lack of blinding or in case of blinding of participants and key study personnel, and unlikely that the blinding could have been broken. We considered that trials were at high risk of bias if no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. Finally, unclear risk of bias if the provided information was insufficient to permit judgement of ‘Low risk’ or ‘High risk’. We assessed blinding separately for different outcomes or classes of outcomes.

- **Blinding of outcomes assessment (checking for possible detection bias)**

For each included trial we noted the methods used, if any, to blind outcome assessors fromknowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes. We assessed methods used to blind outcome assessment as low, high or unclear risk of bias. We considered that trials were at low risk of bias if no blinding of outcome assessment, but we judged that the outcome measurement is not likely to be influenced by lack of blinding or blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. We considered that trials were at high risk of bias if no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome

measurement is likely to be influenced by lack of blinding. Finally unclear risk of bias if the provided information was insufficient to permit judgement of ‘Low risk’ or ‘High risk’.

Incomplete outcome data (checking for possible attrition bias due to de amount, nature and handling of incomplete outcome data)

We described for each included trial, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether trial authors reported attrition and exclusions and the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where trial authors reported or supplied sufficient information, we re-included missing data in the analyses we performed. We assessed methods as low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups); high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; ’as treated’ analysis done with substantial departure of intervention received from that assigned at randomization); or unclear risk of bias. We used a cut-off point of 20% to consider a trial was at low or high risk of bias according to the level of missing data.

Selective reporting (checking for reporting bias)

We investigated the possibility of selective outcome reporting bias in the included trials and reported what we found. We assessed the methods as: low risk of bias (where it was clear that all of the trial’s pre-specified outcomes and all expected outcomes of interest to the review were reported); high risk of bias (where not all the trial’s pre-specified outcomes were reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not used; the trial failed to include results of a key outcome that would have been expected to have been reported); or unclear risk of bias.

Other bias (checking for bias due to problems not covered by above)

We noted any important concerns we had about other possible sources of bias (stopped early due to some data-dependent process or extreme baseline imbalance or has been claimed to have been fraudulent or have been sponsored by industry) (Higgins 2011). We assessed whether each trial was free of other problems that could have put it at risk of bias.

Overall risk of bias

We made explicit judgements about whether trials were at high risk of bias, according to the criteria given in Higgins 2011. With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings.

2.3.4 Measures of treatment effect

Dichotomous data

For dichotomous data, we presented the results as risk ratios (RRs) with 95% confidence intervals (CIs). The RR is used as a relative effect measure, which works well with a low or high rate of events, and is easy to interpret and use in clinical practice.

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardized mean difference to combine trials that measured the same outcome but used different methods.

2.3.5 Unit of analysis issues

We determined which intervention groups were relevant in clinical trials that randomized participants to several intervention groups. In order to avoid confusion for the reader, we included all intervention groups of the trial in the Characteristics of included studies table in the notes cell, provided a detailed description only of the intervention groups relevant to this review and only used these groups in the analyses.

In order to overcome a unit-of-analysis error for trials that contributed multiple, correlated comparisons, we used two approaches: we combined all relevant experimental intervention groups of the trials into a single group and also combined all relevant control intervention groups into a single control group so we could create a single pair-wise comparison (Higgins 2011) when the objective was to compare the experimental branch with any other control group (e.g. imiquimod versus placebo). However, when the objective was to detect differences between experimental groups (e.g. among different imiquimod concentrations), we split the sample of the control group in order to assess the respective comparison (Higgins 2011).

Based on the above, one 3-arm randomized clinical trial (Schofer 2006) compared ablation alone (Group A), imiquimod 5%cream monotherapy (Group B) and combined ablation followed by topical imiquimod (Group C). For the purpose of this systematic review, we only included the relevant experimental (B) and control intervention (A) group (Group A versus B), creating a single pair comparison. Finally, three trials compared two different doses of imiquimod versus vehicle cream, using 1% and 5% imiquimod (Beutner 1998; Edwards 1998) or 2.5% and 3.75% imiquimod (Baker 2011). For these trials, we combined all relevant experimental intervention groups of the trials into a single group in order to create a single pair-wise comparison (Higgins 2011). However, when the target was to detect differences in the experimental groups (e.g. different imiquimod concentrations), we split the sample of the control group (vehicle cream) in order to determine the respective comparison (Higgins 2011).

2.3.6 Dealing with missing data

We identified levels of attrition for included trials and we per-formed analyses for all outcomes, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomized to each group in the analyses, and all participants were analyzed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomized minus any participants whose outcomes were known to be missing. We planned to explore the impact of including trials with high levels of missing data in the overall assessment of treatment effects by using sensitivity analysis but we did not have anadequate number of included trials.

2.3.7 Assessment of heterogeneity

We assessed statistical heterogeneity using the T^2, I^2 statistic and Chi^2 test. We regarded heterogeneity as substantial if the I^2 statistic value was > 40%, and either T^2 was greater than zero or $P < 0.10$ in the Chi^2 test for heterogeneity (Higgins 2011).

2.3.8 Assessment of reporting biases

We planned to explored publication bias through assessment of funnel plot asymmetry and formal tests. For continuous outcomes, we planned to use the test proposed by Egger 1997,

and for dichotomous outcomes we planned to use the test proposed by Harbord 2006. However, we included fewer than ten trials in the meta-analysis so we did not perform these analyses.

2.3.9 Data synthesis

We performed statistical analyses using Review Manager (RevMan). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that trials were estimating the same underlying treatment effect (i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar). If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if we detected substantial statistical heterogeneity, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. We treated the random-effects summary as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful we did not combine trials. Where we used random-effects analyses, we presented the results as the average treatment effect with 95% CIs, and the estimates of the T^2 and I^2 statistic.

2.3.10 Subgroup analysis and investigation of heterogeneity

We proposed to explore the following potential sources of heterogeneity using subgroup analyses:

1. Concentration of imiquimod (less than 5%; 5% or more).
2. Duration of therapy (12 weeks or less; or more than 12 weeks).
3. Times per week (once daily; any other frequency per week).
4. Lesion site (perineal, perianal or other skin site).
5. Sex of the patient.
6. Severity of the disease (area major or minor of 1 cm).

We used the following outcomes in subgroup analyses:

1. Complete regression after treatment.
2. Partial regression at the end of the treatment.
3. Dyspareunia after treatment.

For fixed-effect inverse variance meta-analyses we assessed differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we assessed differences between subgroups by inspection of the subgroups' CIs; non-overlapping CIs indicate a statistically significant difference in treatment effect between the subgroups.

2.3.11 Sensitivity analysis

We planned to explore the impact of the level of bias through undertaking sensitivity analyses (low versus high or unclear risk trials) but the retrieved trials were classified as high risk. Finally, we also planned to explore the change of the point estimate through the inclusion and exclusion of trials with patients that had been previously treated, but the number of retrieved trials recruiting naive population limited this approach: just one trial included a naive population for the comparison between imiquimod versus any other patient-applied treatment (Komericki 2011), and one trial for the comparison of imiquimod versus any other provideradministered treatment (Stefanaki 2008).

2.3.12 Grading the quality of evidence

The GRADE approach specifies four levels of quality (high, moderate, low and very low) starting from high for RCTs (Higgins 2011). Where the included RCTs had quality flaws, we downgraded the quality of evidence by one level depending on the presence of the following factors (Higgins 2011):

1. Study limitations (risk of bias).
2. Inconsistency of results.
3. Indirectness of evidence.
4. Imprecision.
5. Publication bias.

2.3.13 Diferences between protocol and review

During the protocol stage, we stated our intention to explore the duration of therapy (< eight weeks; ≥ eight weeks) and the lesion site (perineal or perianal skin) as potential sources of heterogeneity. However, we discovered two limitations of this approach during data extraction. Firstly, all the included trials provided therapy for longer than eight weeks

(making impossible to perform the subgroup analysis proposed). Secondly, the retrieved studies usually reported by two or more different sites of lesion. Therefore, we re-defined the first subgroup analyses as 12 weeks or less and more than 12 weeks for duration of therapy and we synthesized the other sites reported through a third category named “other lesion site” for the second subgroup. We defined all this adjustments before performing data analysis.

We decided to restrict our subgroup analyses to the principal comparison imiquimod versus placebo because it provided enough clinical trials to perform the analysis. Finally, in order to overcome a unit-of-analysis error, for trials that could contribute multiple, correlated comparisons, we used two approaches: we combined all relevant experimental intervention groups of the studies into a single group and also combined all relevant control intervention groups into a single control group, in order to create a single pair-wise comparison (Higgins 2011) when the objective was compare the experimental branch with any other control group (e.g. imiquimod versus placebo). However, when the objective was to detect differences into the experimental groups (e.g. between different imiquimod concentrations), we split the sample of the control group in order to realize the respective comparison (Higgins 2011).

We planned to explore the impact of the level of bias through undertaking sensitivity analyses (low versus high or unclear risk trials) but all the included trials were classified as high risk, making this impossible. The definition of partial regression after treatment (at least a 50% of clearance of the lesions) was added after the protocol.

Finally, we excluded three studies due to a serious risk of fraud (Syed 1998; Syed 2000; Syed 2002). We considered this as an exclusion criterion, rather than a source of bias.

3. Results[4]

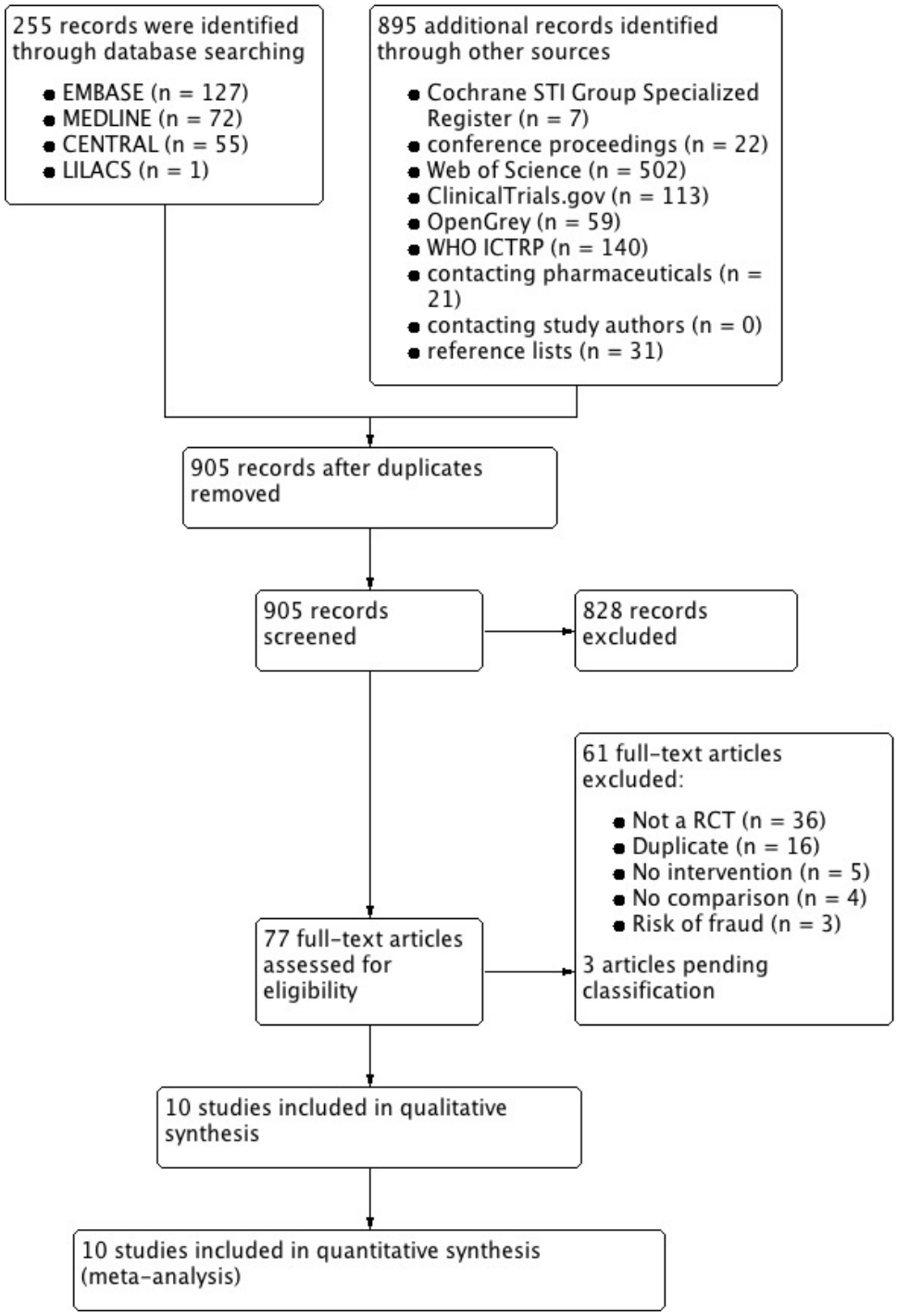
3.1 Description of studies

3.1.1 Results of the search

We retrieved a total of 1150 references and screened 905 after we removed duplicated references. Of these, we initially screened 77 references as RCTs. Ten published trials met our inclusion criteria (Arican 2004; Baker 2011; Beutner 1998; Beutner 1998a; Edwards 1998; Komericki 2011; Padhiar 2006; Schofer 2006; Stefanaki 2008; Tyring 1998; see Figure 3.1). We excluded 61 studies (see Characteristics of excluded studies) and three trials are awaiting classification (Characteristics of studies awaiting classification). Three of the excluded studies contain fraudulent information (Syed 1998; Syed 2000; Syed 2002); the Manager Editor of the STI CRG notified the review authors about this finding.

[4] This document has been published elsewhere as form of the review entitled Imiquimod for anogenital warts in non-immunocompromised adults, published in The Cochrane Library 2014, Issue 11; available on: http://www.thecochranelibrary.com

Figure 3-1: Study flow diagram.



3.1.2 Included studies

The 10 included trials had a total of 1734 participants, with a simple size ranging from 22 to 534 participants. These trials were fromAustria (Komericki 2011), Germany (Schofer 2006), Greece (Stefanaki 2008), India (Padhiar 2006), Turkey (Arican 2004) and USA (Baker 2011; Beutner 1998; Beutner 1998a; Edwards 1998, Tyring 1998). Five were multicentric trials (Baker 2011; Beutner 1998; Beutner 1998a; Edwards 1998; Schofer 2006) and three trials recruited the participants into a sexually transmitted clinic (Komericki 2011; Padhiar 2006; Stefanaki 2008). Three trials implemented a valid method for sample size calculation in advance (Beutner 1998a; Komericki 2011; Schofer 2006). All included trials were published in English.

Population

The included trials recruited men and women aged over 18 years old. However, one trial included participants aged between 15 and 81 years (Baker 2011); another trial that was designed to include people aged over 12 years old ended up recruiting participants aged between 26 and 35 years old (Padhiar 2006); and two trials included only men (Stefanaki 2008) or women (Baker 2011). The most common diagnostic pathway used to confirmed the presence of the condition was the clinician's judgment, but three trials implemented a combination of clinical and histopathological diagnostic (Beutner 1998; Beutner 1998a; Tyring 1998).

The selected trials recruited participants with AGW regardless of their location, shape, size, number or compromised area, except for five trials that implemented some type of exclusion criteria related with the clinical characteristics of the disease. One trial limited the compromised area to 20 cm^2 (Schofer 2006) and three trials used the number of AGWas a inclusion criteria: between two and 30 (Baker 2011) and between two and 50 lesions (Beutner 1998; Edwards 1998; Padhiar 2006).

Finally, seven trials included people with a previous history of treatment (Arican 2004; Baker 2011; Beutner 1998; Beutner 1998a; Edwards 1998; Schofer 2006; Tyring 1998), two trials included naive population (Komericki 2011; Stefanaki 2008) and one trial did not mentioned this characteristic (Padhiar 2006).

Interventions

The most frequently used concentration of imiquimod was 5% (Arican 2004; Beutner 1998a; Komericki 2011; Padhiar 2006; Schofer 2006; Stefanaki 2008; Tyring 1998). However, three trials also assessed other dosages: 2.5%or 3.75%in Baker 2011 and 1% in Beutner 1998 and Edwards 1998.

Eight trials reported an administration frequency of three times per week (Arican 2004; Beutner 1998a; Edwards 1998; Komericki 2011; Padhiar 2006; Schofer 2006; Stefanaki 2008; Tyring 1998) and two trials administrated it daily (Baker 2011; Beutner 1998).

Six trials had a maximum therapy duration of 16 weeks, in two trials the length of the therapy was twelve weeks (Arican 2004; Stefanaki 2008) and in two trials it was eight weeks (Baker 2011; Beutner 1998a). All the included trials established, as an alternative to the length of therapy, the time until complete disappearance of the lesions.

Comparisons

Six trials used a vehicle creamas placebo (Arican 2004; Baker 2011; Beutner 1998; Beutner 1998a; Edwards 1998; Tyring 1998). Two trials compared the effectiveness of imiquimod cream with a patient-applied treatment: podophyllotoxin (Komericki 2011) or podophyllin 20% (Padhiar 2006). In Komericki 2011, participants received treatment twice a day on three consecutive days per week until the warts completely cleared or up to four weeks. In Padhiar 2006, podophyllin was used once a week for maximum of six weeks (Padhiar 2006). Moreover, two trials compared the imiquimod cream with another provider-administered treatment: ablative methods (electrocautery, liquid nitrogen, laser therapy or surgical removal) over a period of four weeks until all visible AGW were removed (Schofer 2006) and cryotherapy once every three weeks for three consecutive sessions (Stefanaki 2008).

Outcomes

Although the included trials reported at least one prespecified primary outcome of this review, there were some differences in reporting and definition of the outcomes between trials. All trial authors reported complete regression of the lesions as the total clearance of the warts. Four trials defined partial regression as at least a 50% of clearance of the lesions (Arican 2004; Beutner 1998; Beutner 1998a; Edwards 1998) and two trials defined it as at

least 75% of clearance of the lesion (Baker 2011; Tyring 1998). Four trials did not evaluate this outcome (Padhiar 2006; Komericki 2011; Schofer 2006; Stefanaki 2008). The included trials also reported time to complete regression, recurrence during follow-up, the appearance of new warts during treatment, and the local or systemic reactions during therapy. We did not obtain any data on the primary outcome dyspareunia after treatment or on the secondary outcomes: relief of symptoms during treatment, excessive scarring, time to resumption of intercourse, pain during therapy, pigmentary changes at application site, requirement of any additional treatment, patient's satisfaction with treatment and cost effectiveness of intervention.

Length of follow-up

The participants were monitored for two (Beutner 1998a), three (Beutner 1998), four (Komericki 2011; Tyring 1998), six (Arican 2004; Padhiar 2006; Schofer 2006) or 12 months (Baker 2011; Edwards 1998; Stefanaki 2008).

3.2 Risk of bias in included studies

We have summarized the risk of bias assessment in Figure 3.2 and Figure 3.3. Also, we provided additional details of the included trials in the Characteristics of included studies tables.

Figure 3-2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

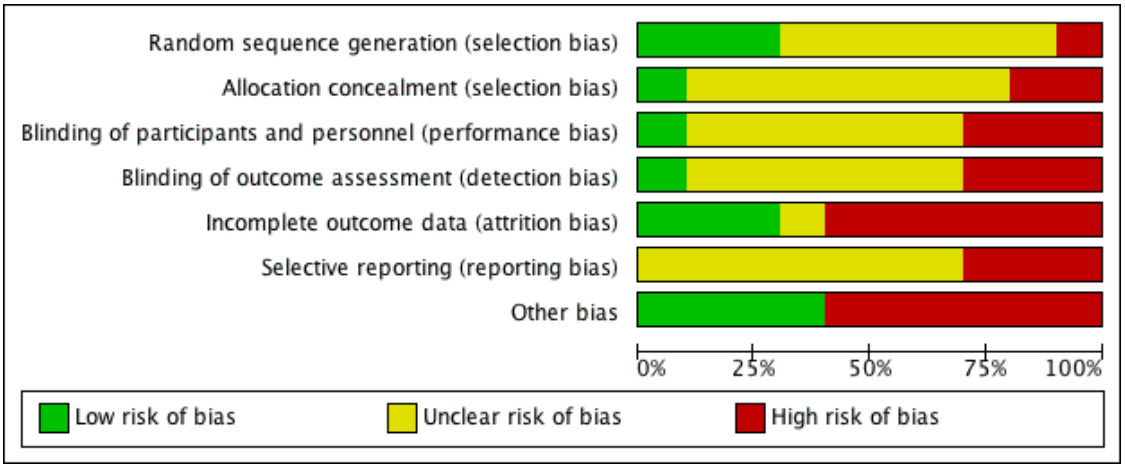
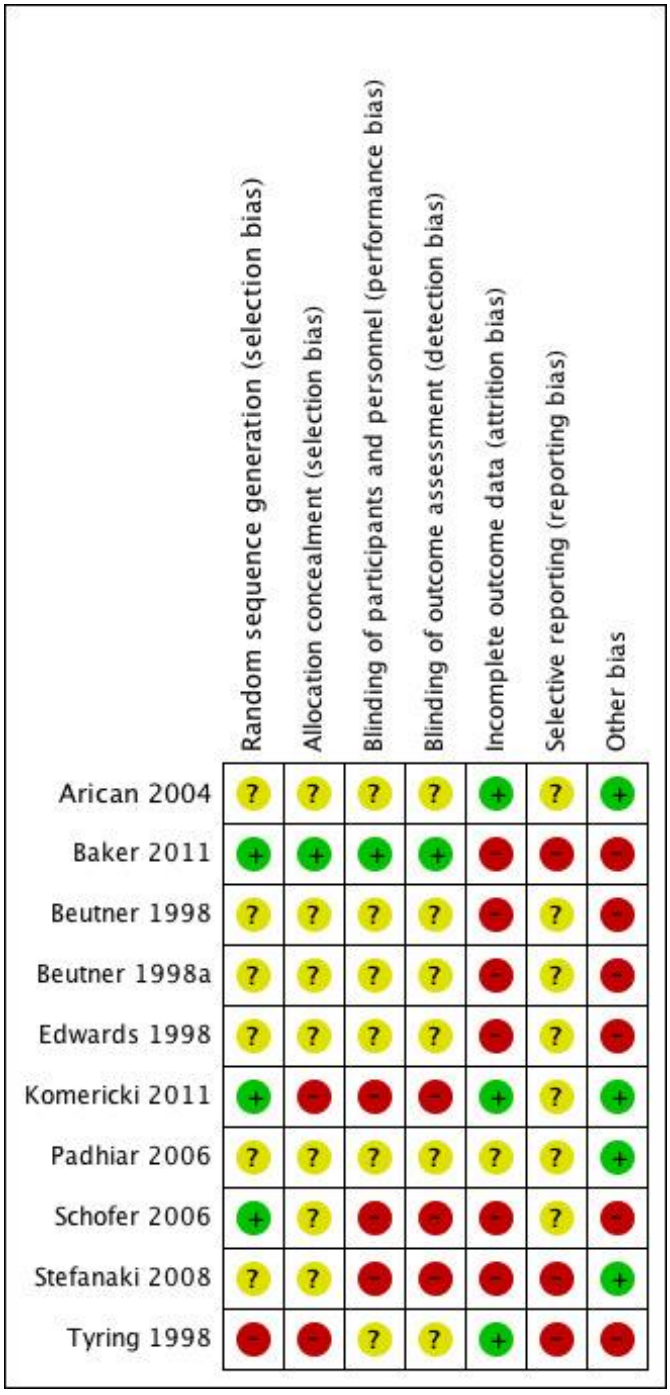


Figure 3-3: Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.



3.2.1 Allocation

Random sequence generation (checking for possible selection bias)

Three trials (Baker 2011; Komericki 2011; Schofer 2006) adequately reported the random sequence generation method by using a computer-generated randomization list, making selection bias at entry unlikely. In Tyring 1998, random sequence generation was broken because two lost participants were directly replaced, making the selection bias likely at entry. The remaining included trials (Arican 2004; Beutner 1998; Beutner 1998a; Edwards 1998; Padhiar 2006; Stefanaki 2008) did not report the randomsequence generation methods, making the risk of selection bias at entry unclear.

Allocation concealment (checking for possible selection bias)

One trial (Baker 2011) implemented sequentially numbered drugs containers as a concealment allocation method, making selection bias at entry unlikely. Komericki 2011 was an open label trial and used a block randomization process (block contained two allocation for each group). As the intervention allocation could have been foreseen, selection bias at entry was likely. Also, Tyring 1998 probably did not implement any allocation concealment method because two lost participants were directly replaced, one to each group, making the selection bias likely. The seven remaining included trials (Arican 2004; Beutner 1998; Beutner 1998a; Edwards 1998; Padhiar 2006; Schofer 2006; Stefanaki 2008) did not report the method used to conceal allocation to interventions prior to assignment, making the risk of selection bias at entry unclear.

3.2.2 Blinding

One trial (Baker 2011) used placebo with identical appearance for the control group to blind trial participants and personnel, making performance bias unlikely. The trial authors assessed two outcomes, complete and partial regression after treatment and recurrence during follow-up, objectively in contrast with outcomes such as pain and any local reactions during therapy, which were subjectively evaluated. However, we judge that the blinding of the outcome assessors fromknowledge of which intervention each participant received prevented detection bias.

Three trials (Komericki 2011; Schofer 2006; Stefanaki 2008) were unblinded to personnel and trial participants and was at high risk of performance bias. We appraised the outcomes complete regression, recurrence during follow-up and appearance of new warts during treatment as at low risk of detection bias. This is because they were objectively assessed and lack of blinding of the outcome assessor was unlikely to affect the results. On the other hand, the trial authors assessed the outcomes pain, local adverse reaction and systemic adverse reaction during therapy, subjectively and the lack of blinding of the outcome assessors from knowledge of which intervention a participant received made detection bias possible.

Six trials (Arican 2004; Beutner 1998; Beutner 1998a; Edwards 1998; Padhiar 2006; Tyring 1998) did not specify how the participants and the personnel were blinded from knowledge of which intervention a participant received, making unclear the risk of performance bias. Appraising for detection bias, the outcomes complete regression after treatment, partial regression after treatment, recurrence during follow-up and appearance of new warts during treatment, were objectively assessed. Lack of blinding of the outcome assessor was unlikely to affect the results. For the outcomes any local reactions during therapy, any systemic reactions during therapy and pain during therapy, the risk of detection bias was unclear because the reports did not provide enough information to judge the risk of bias.

3.2.3 Incomplete outcome data

Three trials (Arican 2004; Komericki 2011; Tyring 1998) appropriately stated the attrition and exclusions at each stage; the reasons were balanced across groups. In addition, the level of missing data was not over 20%and the attrition or exclusion probably was not related with the outcomes, making attrition bias unlikely.

Edwards 1998 had a discontinuation rate and follow-up loss greater than 20%. The trial authors conducted intention-to-treat analysis for efficacy and per protocol analysis for safety outcomes. We appraised it as at high risk of attrition bias.

Stefanaki 2008 performed per protocol analysis, there was over 20% loss to follow-up and the trial authors did not state reasons for it. We judged it at high risk of attrition bias.

Two trials (Baker 2011; Beutner 1998) had missing data greater that 20%, the reasons were stated and they were balanced across trial groups; the authors conducted the analyses only

for those subjects completely treated (per protocol analysis). We assessed these trials as at high risk of bias.

Beutner 1998a did intention-to-treat analysis for one outcome only (complete clearance) and performed per protocol analysis for the remaining six outcomes; withdrawals were fewer than 20%, they were described and balanced between the groups. We appraised this trial as at high risk of attrition bias.

One trial (Schofer 2006) undertook per-protocol analysis; there was under 20% withdrawal but the reasons were not balanced across groups. We considered it as at high risk of attrition bias. Finally, one trial (Padhiar 2006) did not have enough information to permit judgment of “yes” or “no” (rated as “unclear” risk of bias).

3.2.4 Selective reporting

In one trial (Baker 2011) the authors selected time to complete regression as one of the primary outcomes, but this outcome was not mentioned in the results section. Some subgroups which had not been pre-specified were analyzed, as the rate for regression of lesions and the risk of recurrence by age, race, gender, wart area and number of warts. Finally, despite designing the trial to assess the effectiveness and safety of the intervention among male and female (protocols number NCT00674739 and NCT00735462), they reported only those results of the included females. Thus, we judged this trial as at high risk of selective reporting bias.

Another trial (Stefanaki 2008) did not mention the outcome time to regression and recurrence in the methods section, but these outcomes were reported in the outcome section. The trial authors conducted some sub-group analyses and reported them in the results section, but these were not pre-defined or mentioned in the methods section. We judged this trial at high risk of selective reporting bias.

Tyring 1998 stated any systemic reactions as an outcome in the methods section, but the trial authors did not report this outcome in the results section.

For seven trials (Arican 2004; Beutner 1998; Beutner 1998a; Edwards 1998; Komericki 2011; Padhiar 2006; Schofer 2006) the trial protocol is not available and it is unclear if the published reports included all the expected outcomes, including those that were

prespecified. The report had insufficient information to permit judgment of “yes” or “No” (rated as “unclear” risk of bias).

3.2.5 Other potential sources of bias

Six trials had a potential source of bias related to being funded by pharmaceutical companies (Baker 2011; Beutner 1998; Beutner 1998a; Edwards 1998; Schofer 2006; Tyring 1998). The remaining four trials appeared to be free fromother sources of bias (Arican 2004; Komericki 2011; Padhiar 2006; Stefanaki 2008).

3.3 Effects of interventions

See: **Summary of findings for the main comparison** Imiquimod compared to placebo for anogenital warts in non-immunocompromised adults; **Summary of findings 2** Imiquimod compared to any other patient-applied treatment for anogenital warts in non-immunocompromised adults; **Summary of findings 3** Imiquimod compared to any other provider-administered treatment for anogenital warts in nonimmunocompromised adults.

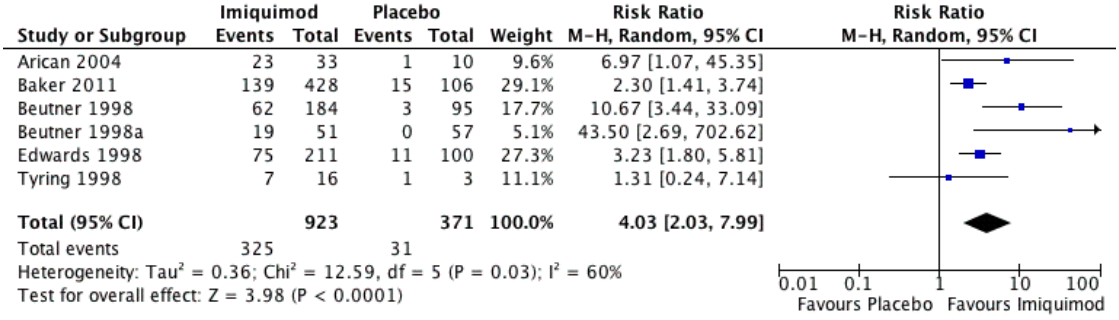
3.3.1 Imiquimod versus placebo

Six trials including 1294 patients compared imiquimod to placebo. However, they did not all contribute data to each outcome.

Complete regression after treatment

The results correspond to the meta-analysis of six trials (Arican 2004; Baker 2011; Beutner 1998; Beutner 1998a; Edwards 1998; Tyring 1998). Imiquimod was associated with a significantly improved complete lesion regression when compared to placebo (RR 4.03, 95% CI 2.03 to 7.99; six trials, 1294 patients, I^2 statistic = 60%; Analysis 1.1; Figure 3.4). The quality of evidence was very low due to the limitations of risk of bias and inconsistency.

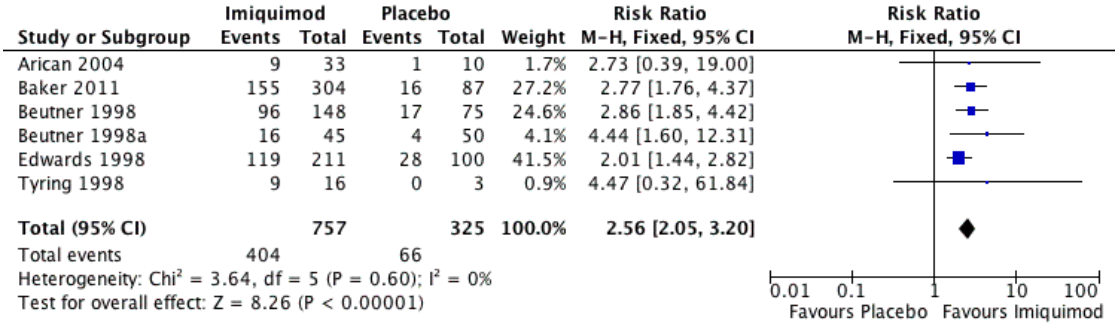
Figure 3-4: Forest plot of comparison: 3.3.1 Imiquimod versus placebo, Analysis 1.1: Complete regression after treatment.



Partial regression after treatment

The results correspond to the meta-analysis of six trials (Arican 2004; Baker 2011; Beutner 1998; Beutner 1998a; Edwards 1998; Tyring 1998). Imiquimod was associated with a significantly improved partial lesion regression when compared to placebo (RR 2.56, 95% CI 2.05 to 3.20; six trials, 1082 patients, I^2 statistic = 0%; Analysis 1.2; Figure 3.5). The quality of evidence was very low due to the limitations of risk of bias and inconsistency.

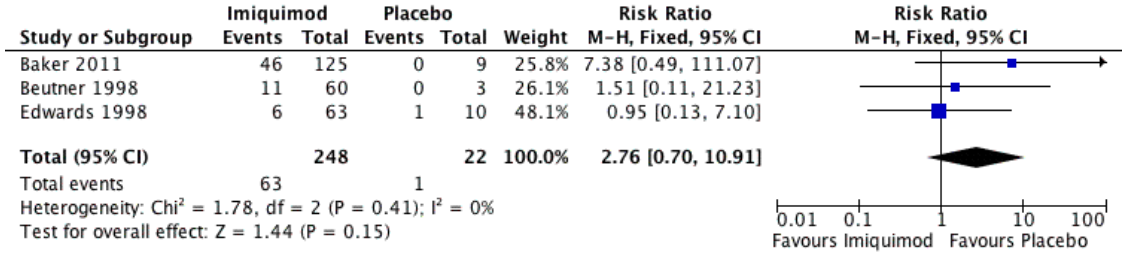
Figure 3-5: Forest plot of comparison: 3.3.1 Imiquimod versus placebo, Analysis 1.2: Partial regression after treatment.



Recurrence during follow-up (from 0 to six months)

The results correspond to the meta-analysis of four trials (Baker 2011; Beutner 1998; Beutner 1998a; Edwards 1998). There was no evidence of a significant difference between placebo and imiquimod in the rate of recurrence of the lesions until six months after treatment (RR 2.76, 95% CI 0.70 to 10.91; three trials, 270 participants, I^2 statistic = 0%; Analysis 1.3; Figure 3.6). The quality of evidence was very low due to the limitations of risk of bias and imprecision.

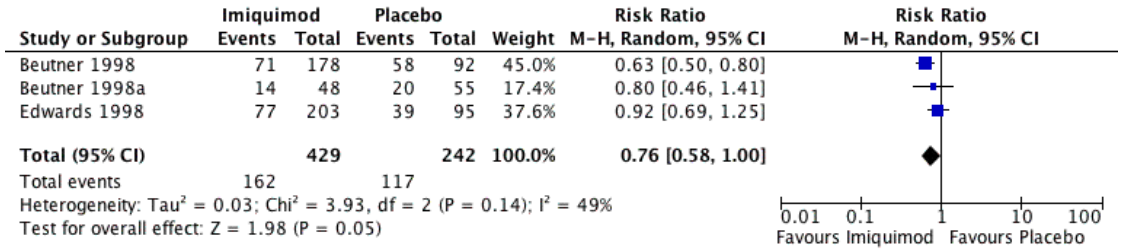
Figure 3-6: Forest plot of comparison: 3.3.1 Imiquimod versus placebo, Analysis 1.3: Recurrence during follow-up from 0 to six months.



Appearance of new warts during treatment

Three trials informed this outcome (Beutner 1998; Beutner 1998a; Edwards 1998). There was no evidence of statistically significance difference between imiquimod and placebo (RR 0.76, 95% CI 0.58 to 1.00; three trials, 671 patients, I^2 statistic = 49%; Analysis 1.4 ; Figure 3.7). The quality of evidence was very low due to the limitations of risk of bias, inconsistency and imprecision.

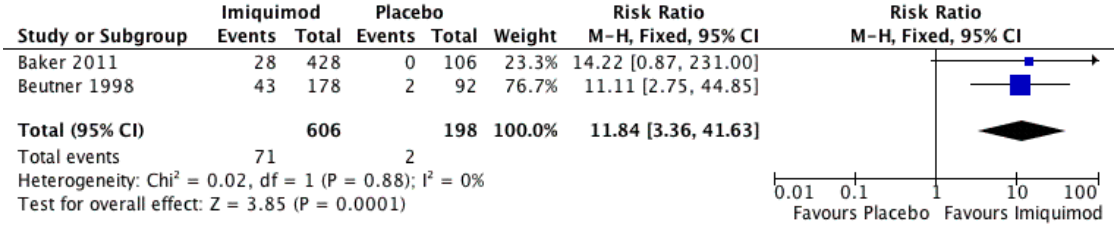
Figure 3-7: Forest plot of comparison: 3.3.1 Imiquimod versus placebo, Analysis 1.4: Appearance of new warts during treatment.



Pain during therapy

The meta-analysis of two trials (Baker 2011; Beutner 1998), showed a significant higher rate of pain with imiquimod compared to placebo (RR 11.84, 95% CI 3.36 to 41.63; two trials, 804 participants, I^2 statistic = 0%; Analysis 1.5; Figure 3.8). The quality of evidence was low due to the limitations of risk of bias.

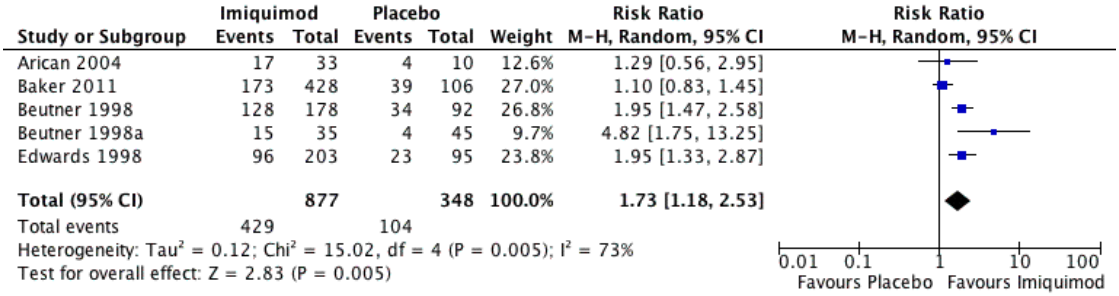
Figure 3-8: Forest plot of comparison: 3.3.1 Imiquimod versus placebo, Analysis 1.5: Pain during therapy.



Any local reaction during therapy

The results correspond to the meta-analysis of five trials (Arican 2004; Baker 2011; Beutner 1998; Beutner 1998a; Edwards 1998). There was a significant higher rate of any local reaction during the therapy with imiquimod compared to placebo (RR 1.73, 95% CI 1.18 to 2.53; five trials, 1225 participants, I^2 statistic = 73%; Analysis 1.6; Figure 3.9). The quality of evidence was very low due to the limitations of risk of bias, inconsistency and imprecision.

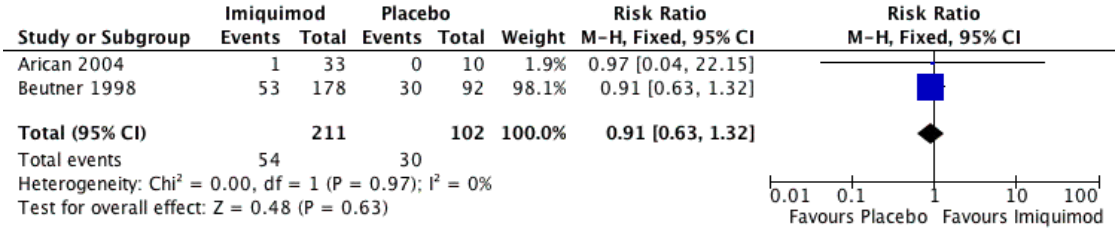
Figure 3-9: Forest plot of comparison: 3.3.1 Imiquimod versus placebo, Analysis 1.6: Any local reactions during therapy.



Any systemic reaction during therapy

There was no evidence of significant difference between placebo and imiquimod in the rate of systemic reactions during the therapy, in the meta-analysis of two trials (Arican 2004; Beutner 1998) (RR 0.91, 95% CI 0.63 to 1.32; two trials, 313 patients, I^2 statistic = 0%; Analysis 1.7; Figure 3.10). The quality of evidence was low due to the limitations of risk of bias and imprecision.

Figure 3-10: Forest plot of comparison: 3.3.1 Imiquimod versus placebo, Analysis 1.7: Any systemic reactions during therapy.



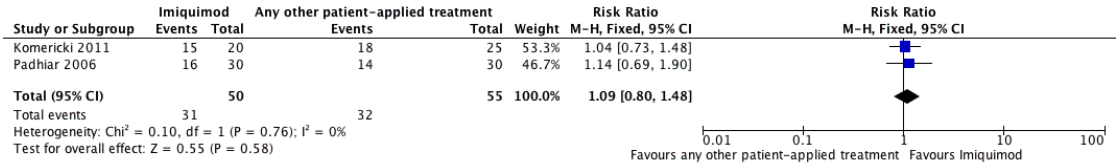
3.3.2 Imiquimod versus any other patient-applied treatment

Two trials including 105 patients compared imiquimod to any other patient-applied treatment (podophyllotoxin and podophyllin) but they did not all contribute data to each outcome.

Complete regression after treatment

The results correspond to meta-analysis of two trials (Komericki 2011; Padhiar 2006). There was no evidence of significant difference between imiquimod and any other patient-applied treatment in the total clearance of the AGW(RR 1.09, 95%CI 0.80 to 1.48; two trials, 105 patients, I^2 statistic = 0%; Analysis 2.1; Figure 3.11). The quality of evidence was very low due to the limitations of risk of bias and imprecision.

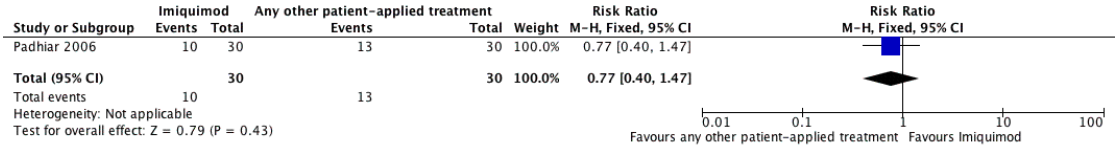
Figure 3-11: Forest plot of comparison: 3.3.2 Imiquimod versus placebo, Analysis 2.1: Complete regression after treatment.



Partial regression after treatment

Only Padhiar 2006 reported on this outcome. There was no evidence of significant difference between imiquimod and any other patient-applied treatment (podophyllotoxin) in the partial regression of the lesions (RR 0.77, 95% CI 0.40 to 1.47; one trial, 60 patients; Analysis 2.2; Figure 3.12). The quality of evidence was low due to the limitations of risk of bias and imprecision.

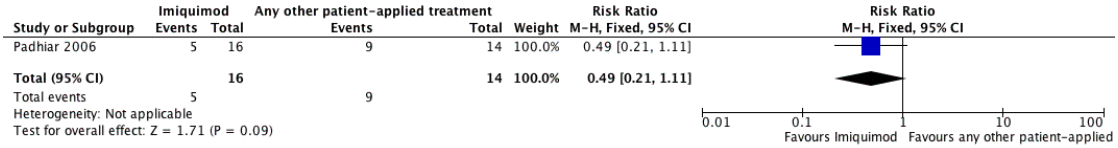
Figure 3-12: Forest plot of comparison: 3.3.2 Imiquimod versus placebo, Analysis 2.2: Partial regression after treatment.



Recurrence during follow-up (from 0 to six months)

The results correspond to one trial (Padhiar 2006). There was no evidence of significant difference between imiquimod and any other patient-applied treatment (podophyllotoxin) in the rate of recurrence of the lesions until six months after treatment (RR0.49, 95%CI 0.21 to 1.11; one trial, 30 participants; Analysis 2.3; Figure 3.13). The quality of evidence was low due to the limitations of risk of bias and imprecision.

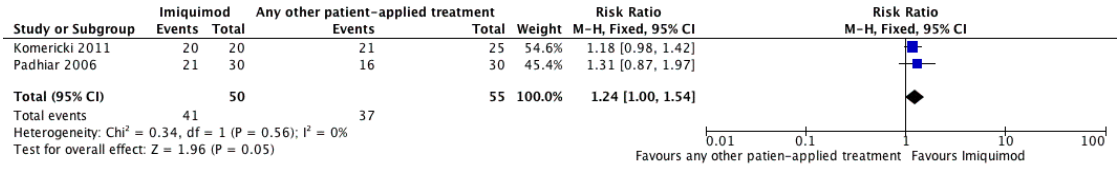
Figure 3-13: Forest plot of comparison: 3.3.2 Imiquimod versus placebo, Analysis 2.3: Recurrence during follow-up from 0 to six months.



Any local reaction during therapy

The results correspond to meta-analysis of two trials (Komericki 2011; Padhiar 2006). There was no evidence of significant difference in the presence of any local reaction during the therapy with imiquimod compared to any other patient-applied treatment (podophyllin 20% and podophyllotoxin) (RR 1.24, 95% CI 1.00 to 1.54; two trials, 105 participants, I^2 statistic = 0%; Analysis 2.4; Figure 3.14). The quality of evidence was very low due to the limitations of risk of bias and imprecision. Any systemic reaction during therapy

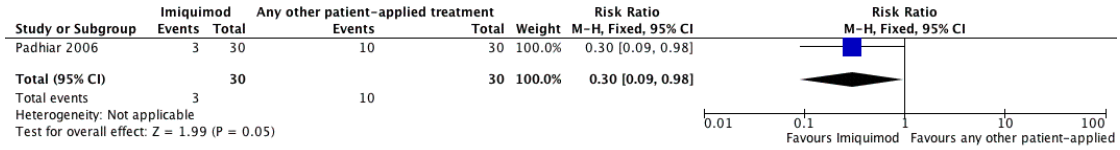
Figure 3-14: Forest plot of comparison: 3.3.2 Imiquimod versus placebo, Analysis 2.4: Any local reactions during therapy.



Any systemic reaction during therapy

One trial reported on this outcome (Padhiar 2006). There were significantly fewer systemic reactions during the therapy with imiquimod compared with any other patient-applied treatment (RR 0.30, 95% CI 0.09 to 0.98; one trial, 60 patients; Analysis 2.5; Figure 3.15). The quality of evidence was low due to the limitations of risk of bias and imprecision.

Figure 3-15: Forest plot of comparison: 3.3.2 Imiquimod versus placebo, Analysis 2.5: Any systemic reactions during therapy.



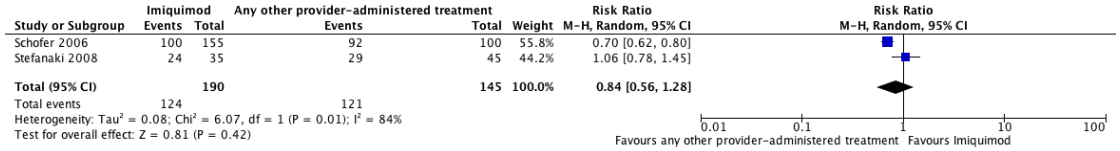
3.3.3 Imiquimod versus any other provider-administered treatment

Two trials (335 patients) compared imiquimod to any other provider-administered treatment (ablative methods and cryotherapy) but they did not all contribute data to each outcome.

Complete regression after treatment

The results correspond to the meta-analysis of two trials (Schofer 2006; Stefanaki 2008). There was no evidence of significant difference between imiquimod and provider-administered treatment in the total clearance of the AGW(RR 0.84, 95%CI 0.56 to 1.28; two trials, 335 patients, I^2 statistic = 84%; Analysis 3.1; Figure 3.16). The quality of evidence was very low due to the limitations of risk of bias, imprecision and inconsistency.

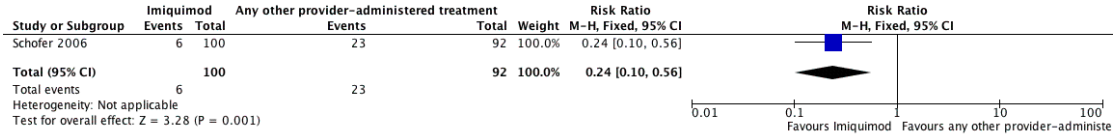
Figure 3-16: Forest plot of comparison: 3.3.3 Imiquimod versus placebo, Analysis 3.1: Complete regression after treatment.



Recurrence during follow-up (from 0 to six months)

The results correspond to one trial (Schofer 2006). There was a significant reduction in the rate of recurrence of the lesions until six months after treatment with imiquimod compared with provideradministered treatment (RR 0.24, 95% CI 0.10 to 0.56; one trial, 192 participants; Analysis 3.2; Figure 3.17). The quality of evidence was very low due to limitations of risk of bias and imprecision.

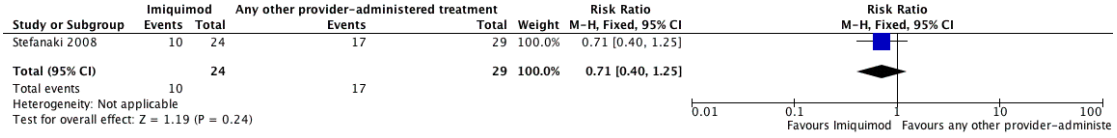
Figure 3-17: Forest plot of comparison: 3.3.3 Imiquimod versus placebo, Analysis 3.2: Recurrence during follow-up from 0 to six months.



Recurrence during follow-up (from six to 12 months)

The results correspond to one trial (Stefanaki 2008). There was no evidence of significant difference in the rate of recurrence of the lesions between six and 12 months after treatment with imiquimod compared with provider-administered treatment (RR 0.71, 95% CI 0.40 to 1.25; one trial, 53 participants; Analysis 3.3; Figure 3.18). The quality of evidence was very low due to the limitations of risk of bias and imprecision.

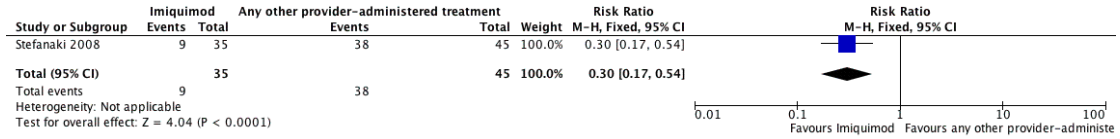
Figure 3-18: Forest plot of comparison: 3.3.3 Imiquimod versus placebo, Analysis 3.3: Recurrence during follow-up from six to 12 months.



Pain during therapy

One trial reported this outcome (Stefanaki 2008). There was less pain during the therapy with imiquimod than with provider-administered treatment (cryotherapy in this trial) (RR 0.30, 95%CI 0.17 to 0.54; one trial, 80 participants; Analysis 3.4; Figure 3.19). The quality of evidence was very low due to the limitations of risk of bias and imprecision.

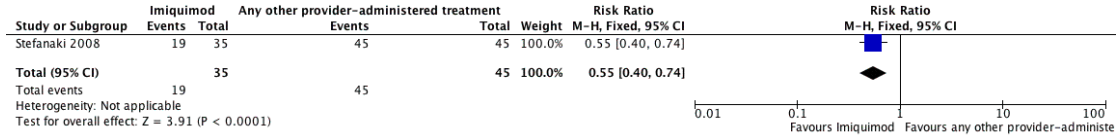
Figure 3-19: Forest plot of comparison: 3.3.3 Imiquimod versus placebo, Analysis 3.4: Pain during therapy.



Any local reaction during therapy

The results correspond to one trial (Stefanaki 2008). There was a significant reduction in the presence of any local adverse reaction during the therapy with imiquimod compared to the provideradministered treatment (cryotherapy in this trial) (RR 0.55, 95% CI 0.40 to 0.74; one trial, 80 participants; Analysis 3.5; Figure 3.20). The quality of evidence was very low due to the limitations of risk of bias and imprecision.

Figure 3-20: Forest plot of comparison: 3.3.3 Imiquimod versus placebo, Analysis 3.5: Any local reactions during therapy.



3.3.4 Subgroup analysis and investigation of heterogenity

We performed subgroup analyses to explore the substantial heterogeneity we found in the analyses “Complete regression” for the comparison imiquimod versus placebo. For this analysis (overall effect I^2 statistic = 60%) we explored whether differences in concentration of imiquimod (less than 5%; 5% or more), duration of therapy (12 weeks or less, or more than 12 weeks), times per week (once daily; any other frequency per week), lesion site (perineal, perianal or any other location) and sex of the patient reduced the heterogeneity in the overall effect size.

Neither of the tests for subgroup effect were significantly different when we explored heterogeneity source by: concentration of imiquimod (P = 0.09; Analysis 4.1), duration of therapy (P = 0.67; Analysis 5.1), times per week (P = 0.92; Analysis 6.1), lesion site (P = 0.37; Analysis 7.1) and sex of the patient (P = 0.11; Analysis 8.1). Subgroup analysis did

not appear to explain the variability in the overall summary effect measures for outcome complete regression, so these findings should be interpreted with caution.

In the analyses “Partial regression” for the comparison imiquimod versus placebo, neither of the tests for subgroup effect showed evidence of statistically significant differences, analyzing by: concentration of imiquimod (P = 0.08; Analysis 9.1), duration of therapy (P = 0.20; Analysis 10.1), times per week (P = 0.38; Analysis 11.1), lesion site (P = 0.83; Analysis 12.1) and sex of the patient (P = 0.66; Analysis 13.1). The effect of the intervention for this outcome did not change according to these population or intervention characteristics. However, this finding should be interpreted with caution based on the very low quality of the evidence.

We did not perform the subgroup analysis “severity of the disease” because none of the included trials provided information on this basal condition. The subgroup analyses were restricted to the comparison of imiquimod versus placebo and the primary outcome: complete and partial regression at the end of the treatment. For the primary outcome dyspareunia after treatment, none of the included trials provided information.

4. Discussion[5]

4.1 Summary of main results

Ten RCTs (1734 participants) met the inclusion criteria. We judged the risk of bias for the included trials to be high. Six trials (1294 participants) compared the use of imiquimod versus placebo. There was very low quality evidence that imiquimod was superior to placebo in achieving complete (RR 4.03, 95%CI 2.03 to 7.99) and partial regression (RR 2.56, 95% CI 2.05 to 3.20). When compared with placebo the effects of imiquimod on recurrence (RR 2.76, 95% CI 0.70 to 10.91), appearance of new warts (RR 0.76, 95% CI 0.58 to 1.00) and frequency of systemic adverse reactions (RR 0.91, 95% CI 0.63 to 1.32) were imprecise. We downgraded the quality of evidence to low or very low. There was low quality evidence that imiquimod led to more local adverse reactions (RR 1.73, 95% CI 1.18 to 2.53) and pain (RR 11.84, 95% CI 3.36 to 41.63).

Two trials (105 participants) compared the use of imiquimod versus any other patient-applied treatment (podophyllotoxin or podophyllin). The estimated effects of imiquimod on complete regression (RR 1.09, 95%CI 0.80 to 1.48), partial regression (RR 0.77, 95%CI 0.40 to 1.47), recurrence (RR 0.49, 95%CI 0.21 to 1.11) or the presence of local adverse reactions (RR 1.24, 95% CI 1.00 to 1.54) were imprecise (very low quality evidence). There was low quality evidence that systemic adverse reactions were less frequent with imiquimod (RR 0.30, 95% CI 0.09 to 0.98).

[5] This document has been published elsewhere as form of the review entitled Imiquimod for anogenital warts in non-immunocompromised adults, published in The Cochrane Library 2014, Issue 11; available on: http://www.thecochranelibrary.com

Finally, two trials (335 participants) compared imiquimod with any other provider-administered treatment (ablative methods and cryotherapy). There was very low quality of evidence that imiquimod did not had a lower frequency of complete regression (RR 0.84, 95% CI 0.56 to 1.28). There was very low quality evidence that imiquimod led to a lower rate of recurrence during sixmonth follow-up (RR 0.24, 95% CI 0.10 to 0.56) but this did not translate in to a lower recurrence from six to 12 months (RR 0.71, 95% CI 0.40 to 1.25; very low quality evidence). There was very low quality evidence that imiquimod was associated with less pain (RR 0.30, 95% CI 0.17 to 0.54) and fewer local reactions (RR 0.55, 95% CI 0.40 to 0.74).

4.2 Overall completeness and applicability of evidence

Although we conducted comprehensive searches to retrieve all published and unpublished RCTs, this systematic review included trials at high risk of bias and consequently with low confidence on the estimate of effect (see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). Additionally, the data are incomplete, and some of the important clinical outcomes were not reported. For example, none of the included trials assessed the frequency of dyspareunia after treatment, the time to complete regression, the relief of symptoms during treatment, the excessive scarring or the pigmentary changes at application site, the requirement of any additional therapy, the patient's satisfaction with treatment or the cost effectiveness of the intervention.

The applicability of the evidence into the target population (men and non-pregnant women with immunocompetence and aged over 16 years) is broad because the retrieved trials were conducted in different clinical settings. The interventions analyzed in the review and the patient-applied treatments (included imiquimod) are available in various clinical settings; contrasting with the provideradministered treatments (e.g. cryotherapy or surgical removal) which require substantial clinical training, additional equipment, local or general anesthesia and longer office visits. When imiquimod was compared with the other patient-applied treatments (e.g. podofilox), imiquimod had the advantage of being an intervention with a minor frequency of systemic side-effects with similar effectiveness.

4.3 Quality of the evidence

We considered the 10 included trials to be at high risk of bias and the confidence in the estimated effect was very low (see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). There is little confidence in the effect estimates; the true effect is likely to be substantially different. The confidence is very low due to trial limitations (lack of blinding, failure to adhere to the intention-to-treat principle, selective reporting and other risk of bias), inconsistency (unexplained variability in some results) and some imprecise results (few women and outcome events with wide CIs). We could not evaluate publication bias, because there were too few included trials into each comparison.

4.4 Potential biases in the review process

We had concerns about publication bias (see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). Publication bias is a possibility because the included trials were mostly funded by industry and due to the limited number of trials for each comparison. It is known that the risk of publication bias is probably higher for reviews that are based on sponsored trials. Another important limitation of this systematic review is the measurement bias present in the available RCTs, especially when the trial authors assessed outcomes subjectively. There was substantial heterogeneity for some outcomes and our investigation of heterogeneity sources (which was based on a small amount of trials for each comparison) could have limited value. Finally, although the trial authors defined by consensus the subgroup analysis of duration of therapy and the lesion site before they carried out the data analysis, these results should be interpreted with caution.

5. Authors' conclussions[6]

5.1 Implications for practice

Due to risk of bias, imprecision and inconsistency for many of the outcomes we have assessed in this Cochrane Review, the benefits and harms of imiquimod compared with placebo should be regarded with caution. The evidence for many of the outcomes that show imiquimod and patient-applied treatment (podophyllotoxin or podophyllin) confer similar benefits but fewer systematic reactions with the Imiquimod, is of low or very low quality. The quality of evidence for the outcomes assessing imiquimod and other provider-administered treatment were of very low quality.

5.2 Implications for research

There is a need for high quality RCTs on treatments for the patients with AGW, particularly comparing imiquimod versus any other patient or provider-administered treatment. Further research should focus on avoiding risk of bias as lack of blinding, failure to adhere to the intention-to-treat principle and selective reporting. Future studies should report important clinical outcomes as: frequency of dyspareunia after treatment, time to complete regression, excessive scarring or the pigmentary changes at application site, the requirement of any additional therapy, the patient's satisfaction with treatment or the cost effectiveness of intervention inter alia.

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[6] This document has been published elsewhere as form of the review entitled Imiquimod for anogenital warts in non-immunocompromised adults, published in The Cochrane Library 2014, Issue 11; available on: http://www.thecochranelibrary.com

A. Appendix 1: Summary of findings[7]

Summary of findings for the main comparison

Imiquimod compared to placebo for AGW in non-immunocompromised adults

Patient or population: AGW in non-immunocompromised adults
Settings: Outpatient
Intervention: Imiquimod
Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk placebo	Corresponding risk Imiquimod			
Complete clearance	Trial population 84 per 1000	352 per 1000 (171 to 671)	RR 4.03 (2.03 to 7.99)	1294 (6 trials)	⊕○○○ very low[1,2]
Partial clearance	Trial population 203 per 1000	535 per 1000 (416 to 652)	RR 2.57 (2.05 to 3.21)	1082 (6 trials)	⊕○○○ very low[1,3]
Recurrence during follow-up from 0 to 6 months	Trial population 45 per 1000	250 per 1000 (32 to 491)	RR 2.76 (0.70 to 10.91)	286 (4 trials)	⊕○○○ very low[4,5]
Appearance of new warts during treatment	Trial population 483 per 1000	378 per 1000 (280 to 483)	RR 0.76 (0.58 to 1.00)	671 (3 trials)	⊕○○○ very low[4,6,7]
Any local reactions during therapy	Trial population		RR 1.73 (1.18 to 2.53)	1225 (5 trials)	⊕○○○ very low[4,7,8]

[7] This document has been published elsewhere as form of the review entitled Imiquimod for anogenital warts in non-immunocompromised adults, published in The Cochrane Library 2014, Issue 11; available on: http://www.thecochranelibrary.com

	299 per 1000	489 per 1000 (353 to 756)			
Any systemic reactions during therapy	Trial population		RR 0.91 (0.63 to 1.32)	313 (2 trials)	⊕⊕◯◯ low[4,7]
	294 per 1000	256 per 1000 (185 to 388)			
Pain during therapy	Trial population		RR 11.84 (3.36 to 41.63)	804 (2 trials)	⊕⊕◯◯ low[4]
	10 per 1000	117 per 1000 (34 to 416)			

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by some limitations on reporting, attrition and other sources of bias.
[2] CIs overlap. Downgraded by some differences on point estimate between trials and substantial heterogeneity ($Tau^2 = 0.36$; Chi^2 test = 12.59, df = 5, P = 0.03; I^2 statistic = 60%).
[3] Downgraded by CIs do not overlap, some differences on point estimate between trials and substantial heterogeneity ($Tau^2 = 0.09$; Chi^2 test = 9.97, df = 5 P = 0.08; I^2 statistic = 50%).
[4] Downgraded by some limitations on attrition and other sources of bias.
[5] Downgraded by low rate of events, not OIS and appreciable harm or benefit.
[6] CIs overlap. No differences on point estimate between trials but downgraded by substantial heterogeneity (heterogeneity: $Tau^2 = 0.03$; Chi^2 test = 3.93, df = 2 (P = 0.14); I^2 statistic = 49%).
[7] Downgraded by appreciable harm or benefit.
[8] Downgraded by CIs do not overlap, some differences on point estimate between trials and substantial heterogeneity ($Tau^2 = 0.12$; Chi^2 test = 15.02, df = 4, P = 0.005; I^2 statistic = 73%).

Additional summary of findings

Imiquimod compared to any other patient-applied treatment for AGW in non-immunocompromised adults

Patient or population: AGW in non-immunocompromised adults
Settings: Outpatient clinic
Intervention: Imiquimod
Comparison: Any other patient-applied treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk any other patient-applied treatment	Corresponding risk Imiquimod			
Complete clearance	Trial population		RR 1.09 (0.80 to 1.48)	105 (2 trials)	⊕○○○ very low[1,2,3]
	582 per 1000	620 per 1000 (466 to 861)			
Partial clearance	Trial population		RR 0.77 (0.40 to 1.47)	60 (1 trial)	⊕⊕○○ low[1,4]
	433 per 1000	333 per 1000 (173 to 637)			
Recurrence during follow-up from 0 to 6 months	Trial population		RR 0.49 (0.21 to 1.11)	30 (1 trial)	⊕⊕○○ low[1,4]
	643 per 1000	313 per 1000 (135 to 714)			
Any local reactions during therapy	Trial population		RR 1.24 (1.00 to 1.54)	105 (2 trials)	⊕○○○ very low[1,2,5]
	673 per 1000	820 per 1000 (673 to 1036)			
Any systemic reactions during therapy	Trial population		RR 0.30 (0.09 to 0.98)	60 (1 trial)	⊕⊕○○ low[1,4]
	333 per 1000	100 per 1000 (30 to 326)			

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by low rate of events, not OIS and appreciable harm or benefit.
[2] Downgraded by some limitations on allocation concealment, performance, detection and reporting bias.
[3] CIs overlap. No differences on point estimate between trials. No substantial heterogeneity (Chi^2 test = 0.10, df = 1, P = 0.76; I^2 statistic = 0%).
[4] Unclear risk for allocation concealment, performance, detection and reporting bias.
[5] CIs overlap. No differences on point estimate between trials. No substantial heterogeneity (Chi^2 test = 0.34, df = 1, P = 0.56; I^2 statistic = 0%).

Imiquimod compared to any other provider-administered treatment for AGW in non-immunocompromised adults

Patient or population: AGW in non-immunocompromised adults
Settings: Outpatient
Intervention: Imiquimod
Comparison: Any other provider-administered treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Any other provider-administered treatment	Imiquimod			
Complete clearance	Trial population		RR 0.84 (0.56 to 1.28)	335 (2 trials)	⊕○○○ very low[1,2,3]
	834 per 1000	653 per 1000 (467 to 1068)			
Recurrence during follow-up from 0 to 6 months	Trial population		RR 0.24 (0.10 to 0.56)	192 (1 trial)	⊕○○○ very low[2,3]
	250 per 1000	60 per 1000 (25 to 140)			
Recurrence during follow-up from 6 to 12 months	Trial population		RR 0.71 (0.40 to 1.25)	53 (1 trial)	⊕○○○ very low[2,3]
	586 per 1000	417 per 1000 (234 to 733)			
Pain during therapy	Trial population		RR 0.30 (0.17 to 0.54)	80 (1 trial)	⊕○○○ very low[2,3]
	844 per 1000	257 per 1000 (143 to 456)			
Any local reactions during therapy	Trial population		RR 0.55 (0.40 to 0.74)	80 (1 trial)	⊕○○○ very low[2,3]
	1000 per 1000	543 per 1000 (400 to 740)			

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] CIs overlap. Downgraded by some differences in point estimates between trials and substantial heterogeneity ($Tau^2 = 0.08$; Chi^2 test $= 6.07$ $P = 0.01$; I^2 statistic $= 84\%$).
[2] Downgraded by low events rate, not OIS and appreciable harm or benefit.
[3] Downgraded by some limitations on performance, detection, attrition and reporting bias.

B. Appendix 2: Characteristics of studies[8]

Tabla 1: Characteistics of included studies.

Arican 2004

Methods	Setting**: Turkey, outpatient clinic** Trial design**: RCT, parallel two arms** Funding sources**: Not reported** Ethical issues**: "Patients that participated in the study provided their consent after they were informed about the treatment options and the course of the study"**
Participants	**Inclusion criteria**: • Volunteer patients • Not received any therapies within the previous three months • 18 years of age or more **Exclusion criteria**: • Patients with a pathological condition • Immunosuppressive or serious systemic disorders • Alcoholics and substance dependent • Frequently recurrent genital herpes • Patients who had undergone a local or systemic therapy within the last three months **Population** **Number of participants**: Total 45 (34 allocated to imiquimod and 11 to placebo). **Mean age (SD)**: IQ5%: 30.3 (6.1). Placebo: 32.3 (6.8). **Site of lesions by sex**: Female: genital: 5, perianal: 5, mixed:1. Placebo: genital: 1, perianal: 1 and mixed: 0; Male: genital: 14, perianal: 7, mixed:1. Placebo: genital: 6, perianal: 1, mixed: 1 **Number of participants who received previous treatment**: Unclear.
Interventions	**Total number of intervention groups**: 2 groups. **Intervention**: Imiquimod 5% cream three times a week, every other day for 12 weeks **Control**: Vaseline cream three times a week, every other day for 12 weeks
Outcomes	During the first examination, regional lesions were determined and mapped, and the localizations and periods of the lesions were recorded. During the duration of the therapy, the lesions were re-assessed re-mapped and the side effects of the drug were investigated.

[8] This document has been published elsewhere as form of the review entitled Imiquimod for anogenital warts in non-immunocompromised adults, published in The Cochrane Library 2014, Issue 11; available on: http://www.thecochranelibrary.com

	When warts were removed, the treatment was interrupted, and the patients were followed-up. At the end of the therapy patients were assessed for recurrences for a period of six months in monthly visits • Complete regression after treatment (total clearance of the warts) • Partial regression after treatment (reduction at least 50% of wart area) • Any local reactions during therapy (erosion, erythema, erythema and erosion, erythema and excoriation, burning sensation or itching) • Any systemic reactions during therapy (influenza-like symptoms)
Notes	Additional information requested from trial authors by e-mail (no answer)

Risk of bias **Bias**	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"This study was planned as randomised, double-blind and placebo-controlled." Comment: No information available to make a judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: No information available to make a judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"This study was planned as randomised, double-blind and placebo-controlled." Comment: No information available to make a judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	omment: Some outcomes did not appear to be affected by blinding issues because they were objectively assessed (complete regression after treatment, partial regression after treatment, recurrence during followup and appearance of new warts during treatment) and they were appraised as low risk of bias. Other outcomes (any local reactions and any systemic reactions) were appraised as unclear risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Losses to follow-up were less than 20%.
Selective reporting (reporting bias)	Unclear risk	Comment: No information available to make a judgement.
Other bias	Low risk	Comment: This trial appears to be free of other sources of bias

Baker 2011

Methods	Setting**: USA, outpatient clinic** Trial design**: Multicentric RCT, parallel three arms** Funding sources**: The trials were supported by Graceway Pharmaceuticals, LLC, Bristol, Tennessee** Ethical issues**: "The studies were conducted in compliance with Good Clinical Practice guidelines and approved by a central institutional review board. All participants provided written informed consent."**
Participants	**Inclusion criteria**: • Women • 12 years or older

	• General good health • 2 to 30 EGWs in the vulvar (including mons), inguinal, perineum, and/or perianal areas. • Minimum total wart area of 10 mm^2 • EGWs were diagnosed clinically; to mimic real world practice, histologic confirmation was not required **Exclusion criteria**: • Human immunodeficency virus infection • Immunosuppression • Other genital infections • Allergy to imiquimod or cream excipients • History of high-risk type HPV infection, high-grade pathology on Papanicolaou smear • Pregnancy or lactation • Imiquimod or HPV vaccination within 1 year, and sinecatechins within 12 weeks, cytotoxics, immunomodulators/immunosuppressives, systemic antivirals (excluding oral anti herpes agents and oseltamivir), investigational therapies and any treatments procedures within the anogenital area within 4 weeks **Population** **Number of participants**: 534 females (212 allocated to imiquimod 2.5%, 216 to imiquimod 3.75% and 106 to placebo) **Mean age**: 33.4 years. **Site of lesions**: "The majority of women (54.5%) had warts on 2 or more anogenital locations; the most frequently involved locations were vulva (64.8%) and perineal (47.9%)." **Number of lesions**: Mean 8.7 **Size of lesions**: Mean 166.3 mm^2 **Number of participants who received previous treatment**: Unclear
Interventions	**Total number of intervention groups**: Three groups **Intervention**: Imiquimod 2.5%, and imiquimod 3.75% cream applied once daily for up to a maximum of 8 weeks **Control**: Vehicle cream applied once daily for up to a maximum of 8 weeks
Outcomes	The trial included a screening visit, an evaluation phase (treatment period of up to 8 weeks and a no-treatment period of up to 8 weeks) of up to 16 weeks, and an observational follow-up phase of up to 12 additional weeks in women with complete clearance. Participants were assessed every 2 weeks during the evaluation phase. Participants with complete clearance of all warts within all anogenital areas entered the 12-week observational follow-up period and were assessed every 4 weeks or until they had a "recurrence" of any wart (baseline or new) in any anogenital area. Spontaneously reported adverse events were collected at each visit • Complete regression after treatment (total clearance of the warts) • Partial regression after treatment (reduction at least 75% of wart area) • Recurrence during follow-up • Pain during therapy • Any local reactions during (erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, and erosion/ulceration)
Notes	Additional information requested from trial authors by e-mail (no answer)

Risk of bias **Bias**	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Identically appearing study kits were prepackaged for each study center according to a computer-generated randomization schedule using a 1:1:2 allocation for placebo, imiquimod 2.5%, and imiquimod 3.75% cream (3 MHealth care, Loughborough, UK) and a block size of 5."

Allocation concealment (selection bias)	Low risk	"The treatment assignment was concealed from the participant, the investigators and their staff, and the clinical research team."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: They used placebo with identical appearing in the control group to blind trial participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Discontinuation rate and loss to follow-up patients were larger than 20% (Figure 3.1). They performed per protocol analysis
Selective reporting (reporting bias)	High risk	Comment: Some not prespecified subgroups (NCT00674739 and NCT00735462) were analyzed, as the rate for regression of lesions and the risk of recurrence by age, race, gender, wart area and number of warts. Finally, in spite of the fact that they designed the trial to assess the effectiveness and safety of the intervention among male and female (NCT00674739 and NCT00735462), they reported only those results of the female included in the trial
Other bias	High risk	Comment: Funded by industry.

Beutner 1998

Methods	Setting**: USA, outpatient clinic** Trial design**: Multicentric RCT, parallel three arms** Funding sources**: The trial was supported by a grant from 3M Pharmaceuticals** Ethical issues**: All patients gave written informed consent before enrollment. The protocol and consent forms were reviewed and approved by appropriate institutional review boards at each institution**
Participants	**Inclusion criteria**: • Otherwise healthy males and females • 18 years and older • At least 2 but not more than 50 external genital warts • Biopsy diagnostic or suggestive of condyloma acuminatum • Bidimensional wart area of at least 10 mm^2 • Seronegative for the human immunodeficiency virus (HIV) • For female patients, not be pregnant or lactating and had to agree to use effective birth-control measures **Exclusion criteria**: • Genital wart therapy in the 4 weeks prior to treatment initiation • For female patients, a pre-trial Pap smear showing a high-grade squamous intraepithelial lesion **Population** **Number of participants**: Total 279 (90 allocated to imiquimod 1% (IQ1%), 94 to imiquimod 5% (IQ5%) and 95 to placebo) **Mean age (SD)**: IQ5%: 30(10), IQ1%: 33(11) Vehicle: 30 (9).

	Site of lesions: "The primary locations of warts in the female patients were vulva (88%) and/or perianal (47%), and in men they were penile (90%) and/or perianal (14%)." **Number of lesions**: Median (range). IQ5%: 7 (1 to 47). IQ1%: 8 (1 to 50).Vehicle: 8 (1 to 45) **Size of lesions**: Median mm^2 (range). IQ5%: 137 (2 to 9588). IQ1%: 148 (10 to 13461). Vehicle: 121 (4 to 2603) **Number of participants who received previous treatment**: 201; (IQ5%: 63, IQ1%: 66, Vehicle: 72).
Interventions	**Total number of intervention groups**: three groups. **Intervention**: Imiquimod 5% cream daily for a maximum of 16 weeks. A second group received 1% imiquimod 1% cream daily for a maximum of 16 weeks **Control**: Vehicle cream daily for a maximum of 16 weeks.
Outcomes	During the 8-week treatment period, patients made one initiation visit and seven oncea-week interval visits. At these visits, wart evaluations, skin irritation assessments and vital sign measurements were recorded. Patients were queried regarding adverse events at the site of cream application or adjacent areas. Objective evidence of inflammation at the site of cream application and at adjacent sites was evaluated. Patients who experienced complete clearing of warts during the treatment period entered into a treatment free follow-up period of up to 10 weeks or until recurrence was noted. Patients who had a partial response at the end of the 8-week treatment period were evaluated again at week 2 of follow-up to determine whether they had achieved complete clearing • Complete regression after treatment (total clearance of the warts) • Partial regression after treatment (reduction at least 50% of wart area) • Recurrence during follow-up • Appearance of new warts during treatment • Pain during therapy • Any local reactions during (erythema, burning, irritation, tenderness, ulceration, erosion, itching) • Any systemic reactions during therapy (not mentioned and there were no serious systemic adverse reactions reported in either group)
Notes	Additional information requested from trial authors by e-mail (no answer)

Risk of bias **Bias**	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised by study centre and gender to receive…" Comment: No information available to make a judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: No information available to make a judgement.
Blinding of participants and personnel (performance bias) *All outcomes*	Unclear risk	"double-blind, randomised, parallel-group study assessed…" Comment: No information available to make a judgement.
Blinding of outcome assessment (detection bias) *All outcomes*	Unclear risk	Comment: Some outcomes did not appear to be affected by blinding issues because they were objectively assessed (complete regression after treatment, partial regression after treatment, recurrence during followup time to complete regression and appearance of new warts during treatment) and they were appraised as low risk of bias. Other outcomes (pain, any local reactions and any systemic reactions) were appraised as unclear risk of bias

Incomplete outcome data (attrition bias) All outcomes	High risk	"Of the 279 patients, 72 (26%) did not complete treatment (25 in the 5% imiquimod cream group, 19 in the 1% imiquimod cream group, and 28 in the vehicle group)" Comment: Number of withdrawals is large enough to influence effect estimates. Per protocol analysis
Selective reporting (reporting bias)	Unclear risk	Comment: No information available to make a judgement.
Other bias	High risk	Comment: Funded by industry.

Beutner 1998a

Methods	Setting**: USA, outpatient clinic** Trial design**: Multicentric randomized clinical trial, parallel two arms** Funding sources reported**: Yes, the trial was supported by 3M Pharmaceuticals.** Ethical issues**: Informed consent and review board per center.**
Participants	**Inclusion criteria**: • HIV seronegative • Neither lactating nor pregnant • More than 18 years old **Exclusion criteria**: • Women with vaginal warts or low- or high-grade cervical squamous intraepithelial **Population** **Number of participants**: Total 108 (51 allocated to imiquimod and 57 to placebo) **Mean age**: 29 years for imiquimod, 30 years for vehicle. **Site of lesions**: genital: men (predominantly 91% on the shaft of the penis) and women (vulva, perineal, and perianal areas, the mons pubis and thigh). Some subject had warts at multiple sites **Number of participants who received previous treatment**: 74/108 (Imiquimod 35/51, Vehicle 39/57).
Interventions	**Total number of intervention groups**: Two groups. **Intervention**: Imiquimod 5% three times weekly for up to 8 weeks. **Control**: Physically indistinguishable cream three times per week for up to 8 weeks
Outcomes	Patients were evaluated weekly for the first 4 weeks and every 2 weeks there after for the remainder of the 16-week treatment period as well as during the 12-week follow-up period. A detailed wart assessment, including photographs, measurements, counts, and location, was completed before the trial treatment was initiated and at each evaluation visit. New warts that developed during the treatment period were treated with trial medication and were followed separately from the baseline target warts. Both the patient and trial personnel assessed local skin reactions at the treatment sites. All patients were asked about adverse experiences at each evaluation visit • Complete regression after treatment (total clearance of the warts) • Partial regression after treatment (reduction at least 50% of wart area) • Recurrence during follow-up (from 0 to six months) • Appearance of new warts during treatment • Local reactions during therapy (erythema, excoriation or flaking, erosion, edema, scabbing, induration, ulceration, vesicles)
Notes	Additional information requested from trial authors by e-mail (no answer)

Risk of bias **Bias**	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection	Unclear risk	"This study was a double-blind, randomised, placebo-controlled,

bias)		parallel design conducted at three centres." Comment: No information available to make a judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: No information available to make a judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Blinding was described as "double-blinded" and did not specify who. No information available to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Some outcomes did not appear to be affected by blinding issues because they were objectively assessed (complete regression after treatment, partial regression after treatment, recurrence during followup, time to complete regression and appearance of new warts during treatment) and they were appraised as low risk of bias. Other outcomes (pain, any local reactions and any systemic reactions) were appraised as unclear risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Intention-to-treat analysis was performed only for one out of seven outcomes (complete clearance)
Selective reporting (reporting bias)	Unclear risk	Comment: No information available to make a judgement.
Other bias	High risk	Comment: Funded by industry.

Edwards 1998

Methods	Setting**: USA and Canada, outpatient clinic** Trial design**: Multicentric randomized clinical trial, parallel, three arms** Funding sources**: The trial was supported by 3M pharmaceuticals.** Ethical issues**: Ethical board and sign consent.**
Participants	**Inclusion criteria**: • Healthy men and women • 18 years or older • 2 to 50 external lesions, the total wart area was no less than 10 mm • Biopsy (diagnostic or suggestive) no dysplasia • No treatment 4 weeks before enrollment **Exclusion criteria**: • High-grade squamous intraepithelial lesions • Patients immunosuppressed • Pregnant or lactating women • Chemical or alcohol dependency • Skin disease • Any local drug 2 weeks before enrollment **Population** **Number of participants**: Total 311 (102 allocated to imiquimod 1%, 109 to imiquimod 5% and 100 to placebo) **Mean age (SD)**: IQ5%: 32 (12). IQ1%: 30 (10). Vehicle: 31 (10). **Size of lesions**: Median mm^2 (range). IQ5%: 69 (8 to 5525). IQ1%: 74 (10 to 4271). Vehicle: 77 (7 to 5000) **Number of participants who received previous treatment**: Unclear.
Interventions	**Total number of intervention groups**: Three groups. **Intervention**: Imiquimod 5% or 1%. 3 times each week until complete clearance or for a maximum of 16 weeks

	Control: Patients self-applied vehicle cream 3 times until complete clearance or for a maximum of 16 weeks
Outcomes	During the first examination, regional lesions were determined and mapped, and photographed. During the treatment phase of the trial, the patients were seen weekly for 2 weeks and the biweekly until their warts cleared of the remainder of the 16 week treatment period. During each visit, patient diaries were checked and patients were questioned for adverse reactions. Warts were measured and photographed and the area was examined for signs and symptoms of local inflammation • Complete regression after treatment (total clearance of the warts) • Partial regression after treatment (reduction at least 50% of wart area) • Recurrence during follow-up • Appearance of new warts during treatment • Any local reactions during (erythema, erosion, excoriation or flaking, edema, scabbing, induration)
Notes	Additional information requested from trial authors by e-mail (no answer)

Risk of bias **Bias**	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"…patients were randomised to use 1 of 3 treatments…" Comment: No information available to make a judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: No information available to make a judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Randomized, double-blind, placebo-controlled comparison…" Comment: No information available to make a judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Some outcomes did not appear to be affected by blinding issues because they were objectively assessed (complete regression after treatment, partial regression after treatment, recurrence during followup and appearance of new warts during treatment) and they were appraised as low risk of bias. Other outcomes (any local reactions and any systemic reactions) were appraised as unclear risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	"Seventy-seven patients discontinued use of medication during the study, and the discontinuation rate was similar for each group" Comment: 25% withdrawals
Selective reporting (reporting bias)	Unclear risk	Comment: No information available to make a judgement.
Other bias	High risk	Comment: Funded by industry.

Komericki 2011

Methods	Setting**: Austria, outpatient clinic** Trial design**: Single center, randomized clinical trial. Parallel two arms** Funding sources**: The trial was not funded by any drug manufacturer** Ethical issues**: Informed consent**

Participants	**Inclusion criteria**: • Never treated for AGW **Exclusion criteria**: • Age below 18 years • Immunosuppression • Pregnancy • Breast-feeding • Involvement of the anal canal • Severe disease requiring surgery **Population** **Number of participants**: Total 45 (20 allocated to imiquimod and 25 to podophyllotoxin) **Mean** **age**: 30 years **Site of lesions**: Genital 60%; anal 20% and anogenital 20% **Number of participants who received previous treatment**: Not mentioned
Interventions	**Total number of intervention groups**: Two groups. **Intervention**: Imiquimod 5%, three times per week until complete clearance or up to 16 weeks **Control**: Podophyllotoxin 0,5%, two times on three consecutive days per week until complete clearance or up to 4 weeks
Outcomes	Efficacy (primary endpoint) was assessed at the end of treatment, 5 weeks after the start of podophyllotoxin and 16 weeks after the start of imiquimod. Side effects (secondary endpoint) were assessed at each check up, 2 weeks after the start and at the end of podophyllotoxin treatment; and 4, 8, 12 and 16 weeks after the start of imiquimod therapy • Complete regression after treatment (total clearance of the warts) • Any local reactions during therapy (erythema/inflammation, erosions, erythema/inflammation plus erosions)
Notes	No additional information requested from trial authors.

Risk of bias **Bias**	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Allocation to treatment groups was done according to a ranking, which was created by block randomisation. Each block contained 4 items (2X imiquimod and 2X podophyllotoxin) to assure a balanced design with equal group sizes" Comment: Probably done. Lowrisk of bias.
Allocation concealment (selection bias)	High risk	Comment: The trial was an open label trial and realized a block randomization process been possible that the intervention allocation could have been foreseen in advance making selection bias at entry likely
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial was an open label trial and the authors mentioned during the trial "A potential bias might result from lack of blinding patients and clinicians as to the treatment assignment"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: Unblinded to personnel and trial participants making likely the risk for performance bias. The outcomes complete regression, recurrence during followup and appearance of new warts during treatment were appraised as low risk for detection bias because were

		outcomes objectively assessed and we judge that the lack of blinding of the outcome assessor is unlikely to affect the results. On the other hand, the outcomes pain, local reaction and systemic reaction during therapy, were assessed subjectively and we judge that the lack blinding of the outcome assessors from knowledge of which intervention a participant received make possible the detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Six patients were lost to follow-up, 5 in the imiquimod, and 1 in the podophyllotoxin group" Comment: Missing outcome data balanced across groups and less than 20% of missing data
Selective reporting (reporting bias)	Unclear risk	Comment: No information available to make a judgement.
Other bias	Low risk	Comment: This trial appears to be free of other sources of bias

Padhiar 2006

Methods	Setting**: India, outpatient clinic** Trial design**: Single center randomized clinical trial, parallel two arms** Funding sources**: Not reported** Ethical issues**: Not stated**
Participants	**Inclusion criteria**: • Clinical diagnosis of AGW • At least two but not more than 50 warts **Exclusion criteria**: • HIV **Population** **Number of participants**: Total 60 (30 allocated to imiquimod and 30 to placebo) from 26 to 35 years old **Site of lesions**: In males were located predominantly on penis and in females, were located on vulva (50%) followed by 16.6% in perianal area **Number of lesions**: Imiquimod 5%: 105 total warts. Podophyllin 20%: 90 total warts **Size of lesions**: Imiquimod 5%: 2100 mm^2 and podophyllin 20%: 2500 mm. **Number of participants who received previous treatment**: Not mentioned.
Interventions	**Total number of intervention groups**: Two groups. **Intervention**: Imiquimod 5% cream three times each week until all baseline warts disappeared or for 16 weeks **Control**: Podophyllin 20% once in a week for maximum up to 6 weeks.
Outcomes	During the first examination, regional lesions were determined and mapped, and the localizations and periods of the lesions were recorded. During the duration of the therapy, the lesions were re-assessed re-mapped and the side effects of the drug were investigated. When warts were removed, the treatment was interrupted, and the patients were followed-up. At the end of the therapy patients were assessed for recurrences for a period of six months by quarterly visits • Complete regression after treatment (total clearance of the warts) • Recurrence during follow-up from 0 to 6 months • Any local reactions during therapy (erythema, edema, induration, ulceration, itching and vesiculation)

	• Any systemic reactions during therapy (headache, diarrhea, influenza-like symptoms)
Notes	Additional information requested from the trial authors by e-mail (no answer)

Risk of bias **Bias**	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised to receive …" Comment: No information available to make a judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: No information available to make a judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No information available to make a judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Some outcomes did not appear to be affected by blinding issues because they were objectively assessed (complete regression after treatment, recurrence during follow-up) and they were appraised as low risk of bias. Other outcomes (any local reactions and any systemic reactions) were appraised as unclear risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: The authors did not reported the attrition and exclusions in sufficient detail to allow an assessment
Selective reporting (reporting bias)	Unclear risk	Comment: No information available to make a judgement.
Other bias	Low risk	Comment: This trial appears to be free of other sources of bias

Schofer 2006

Methods	Setting**: Germany, outpatient clinic** Trial design**: Multicentric randomized clinical trial, parallel, 3 arms** Funding sources**: The trial was supported by 3M Medica, Neuss, Germany** Ethical issues**: The trial was approved by the local ethics committees. Informed consent**
Participants	**Inclusion criteria**: • Participants of both gender over 18 years • External AGW with maximum extension area of 2000 mm^2 • Maximum height of single AGW less than 1 cm **Exclusion criteria**: • Imiquimod 5% cream within the previous 6 months • Any other AGW therapy within 4 weeks prior • Inflammatory skin conditions within the target area • Autoimmune diseases or immunosuppression • Pregnant or lactating females **Population** **Number of participants**: Total 358 (100 allocated to ablation alone, 155 to imiquimod and 103 to ablation followed by imiquimod) **Mean age**: 33.1 years (range 18 to 73). **Site of lesions**: "The most common location of genital warts was the foreskin/glans penis and the penis shaft in males and the vulva in females"

	Size of lesions: Mean mm^2 (range): Ablation 142.2 mm^2 (4 to 1960), imiquimod: 105. 5 mm^2 (1 to 1912), ablation + imiquimod: 180.3mm^2 (2 to 1354). **Number of participants who received previous treatment**: 153 (Ablation: 36, imiquimod: 68, and ablation + imiquimod: 49 participants)
Interventions	**Total number of intervention groups**: Three. Ablation, imiquimod, and ablation + imiquimod. **Intervention**: Imiquimod 5%3 times peer week before bedtime until complete clearance or for a maximum of 16 weeks **Comparison**: The subjects were treated depending on which ablative method was practiced by the investigator: electrocautery, liquid nitrogen, laser therapy or surgical removal. The procedure could be repeated over a period of 4 weeks until all visible AGW were removed. The third group received ablation plus imiquimod. The participants had an ablative procedure and after complete clearance and wound healing, started an adjuvant treatment with imiquimod 5%
Outcomes	The trial consisted of a treatment phase and a 6-month follow-up period. The primary efficacy parameter was the observed sustained clearance at month three of the treatmentfree follow-up period. Additionally, subjects were assessed after 4 weeks and at 6 months post-treatment for sustained clearance/recurrences. The investigators assessed the safety of the imiquimod treatments at each control visit by documenting the presence of local skin reactions. Subjects reported any symptoms like itching, burning or pain • Complete regression after treatment (total clearance of the warts) • Recurrence during follow-up from 0 to 6 months • Local reactions (erythema, edema, induration, vesicles, erosion, ulceration, flaking or scabbing)
Notes	Additional information requested from the trial authors by e-mail (no answer)

Risk of bias **Bias**	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: The trial adequately reported the random method generation by using the RPAS 3 program, Version 1.52, a part of the EQUILA software package of Episys Ltd
Allocation concealment (selection bias)	Unclear risk	Comment: No information available to make a judgement.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This trial was an open label trial.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: Unblinded to personnel and trial participants making likely the risk for performance bias. The outcomes complete regression, recurrence during followup and appearance of new warts during treatment were appraised as low risk for detection bias because were outcomes objectively assessed and we judge that the lack of blinding of the outcome assessor is unlikely to affect the results. On the other hand, the outcomes pain, local reaction and systemic reaction during therapy, were assessed subjectively and we judge that the lack blinding of the outcome assessors from knowledge of which

		intervention a participant received make possible the detection bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: Per protocol analysis.
Selective reporting (reporting bias)	Unclear risk	Comment: No information available to make a judgement.
Other bias	High risk	Comment: Funded by industry.

Stefanaki 2008

Methods	Setting**: Greece, outpatient clinic** Trial design**: Single center randomized clinical trial, parallel two arms** Funding sources**: Not reported** Ethical issues**: The trial protocol was approved by the Institutional Review Board. Informed consent was obtained**
Participants	**Inclusion criteria**: • Immunocompetent male patients • First diagnosed with external genital and perianal warts • No patient had undergone any type of treatment for AGW prior to enrollment **Exclusion criteria**: • Bowenoid papulosis • Severe medical condition (haematological, hepatic-hepatitis B or C, neurological, renal, endocrine, collagen and gastrointestinal). • Drug or alcohol dependency **Population** **Number of participants**: 80 males (35 allocated to imiquimod and 45 to cryotherapy). Mean age (SD). IQ5%: 31.8 (10.8). Cryotherapy: 30.7 (12.2) **Site of lesions**: IQ5%: genital 26 (74.3%), anal 7 (20%) and anogenital 2 (5.7%) Cryotherapy: genital 39 (86.7%), anal 3 (6.7%) and anogenital 3 (6.7%) **Number of lesions**: IQ5%: 1 to 10 lesions (57%), > 10 (43%). Cryotherapy: 1 to 10 lesions (65%). > 10 (35%) **Shape of lesions**: IQ5%: Penduculated 20 (57.1%). Papular 3 (8.6%). Criotherapy: Penduculated: 9 (20%). Papular: 18 (40%) **Size of lesions**: IQ5%: = 2 cm^2: 21 (60%). > 2 cm2: 14 (40%). Cryotherapy: = 2 cm : 19 (42%). > 2 cm^2: 26 (57.8%). Number of participants who received previous treatment: None
Interventions	**Total number of intervention groups**: 2 groups. **Intervention**: Imiquimod 5% cream three times a week for twelve weeks. **Control**: Cryotherapy once in three weeks for three consecutive sessions
Outcomes	At the initial visit prior to treatment, the baseline warts were photographed and measured and the exact number of warts, their location, morphology, color and duration were recorded. Follow-up appointments were arranged every month for the first three months and after six and 12 months, or in between whenever the patients noticed any signs of recurrence. During the treatment period, at each visit, warts were measured and photographed and any local or adverse systemic reactions were documented • Complete regression after treatment (total clearance of the warts) • Recurrence during follow-up from 0 to 6 months • Pain during therapy • Any local reactions during therapy (erythema, oedema, erosions, ulceration and fever) • Any systemic reactions during therapy (fever)
Notes	Additional information requested from the trial authors by e-mail (no answer)

Risk of bias **Bias**	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	"Patients were randomised to receive either…" Comment: No information available to make a judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: No information available to make a judgement.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: This trial was a open label trial.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: Unblinded to personnel and trial participants making likely the risk for performance bias. The outcomes complete regression, recurrence during followup and appearance of new warts during treatment were appraised as low risk for detection bias because these outcomes were objectively assessed and we judged that the lack of blinding of the outcome assessor is unlikely to affect the results. On the other hand, the outcomes pain, local reaction and systemic reaction during therapy, were assessed subjectively and we judged that the lack blinding of the outcome assessors from knowledge of which intervention a participant received make possible the detection bias
Incomplete outcome data (attrition bias) All outcomes	High risk	"15 patients from the imiquimod group (30%) and 25 patients from the cryotherapy (64,2%) group were either lost from follow-up or did not provide analyzable data" Comment: Substantial numbers of missing and per protocol analysis
Selective reporting (reporting bias)	High risk	Comment: During the materials and methods sections, the authors did not mention time to complete clearance and partial clearance as primary or secondary outcomes, but they reported this in the results section
Other bias	Low risk	Comment: This trial appears to be free of other sources of bias

Tyring 1998

Methods	Setting**: No information about country or setting** Trial design**: Randomized clinical trial, parallel, two arms** Funding sources**: The trial was supported by 3M Pharmaceuticals** Ethical issues**: Informed consent was obtained from each patient**
Participants	**Inclusion criteria**: • 18 ys old or older • Histologically confirmed diagnosis • Patients had to have at least ten but no more than 50 warts prior to pre-trial biopsy **Exclusion criteria**: • HIV • High-grade cervical intraepithelial lesions • Previously treated with imiquimod or, within 4 weeks of the trial, received IFN,

	an IFN-inducer, an immunomodulator, oral or topical antiviral drugs, cytotoxic or investigational drugs, or chemical and/or surgical wart therapy • Any topical non-wart therapy to the wart site, or oral or inhaled corticosteroids within 2 weeks of the trial were also ineligible **Population** **Number of participants**: 22 (16 allocated to imiquimod and 6 to placebo). **Age of participants**: No data **Site of lesions**: No data **Number of participants who received previous treatment**: Unclear.
Interventions	**Total number of intervention groups**: Two groups. **Intervention**: Imiquimod 5% cream three times per week for a maximum of 16 weeks **Control**: Vehicle cream three times per week for a maximum of 16 weeks
Outcomes	Patients were seen every 2 weeks until their target warts cleared or up through 16 weeks of treatment, whichever occurred first • Complete regression after treatment (total clearance of the warts) • Partial regression after treatment (reduction at least 75% of wart area)
Notes	Additional information requested from the trial authors by e-mail (no answer)

Risk of bias **Bias**	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"Patients were stratified by gender and randomized to imiquimod cream 5% or vehicle in a 4:1 ratio" Comment: The random sequence generation was broken because two lost participants were directly replaced, making the selection bias likely at entry
Allocation concealment (selection bias)	High risk	Comment: The random sequence generation was broken because two lost participants were directly replaced, making the selection bias likely at entry
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: No information available to make a judgement.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Some outcomes did not appear to be affected by blinding issues because they were objectively assessed (complete regression after treatment, partial regression after treatment) and they were appraised as low risk of bias. Other outcome (any systemic reactions) was appraised as unclear risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Losses to follow-up were less than 20%.
Selective reporting (reporting bias)	High risk	Comment: During background section, the authors mentioned systemic reaction but not reported during outcome section
Other bias	High risk	Comment: Funded by industry.

Tabla 2: Characteistics of excluded studies.

Study	Reason for exclusion
Alam 2001	Not a RCT.
Ankerst 2009	Not a RCT.
Arany 1999	Duplicate from Tyring 1998.
Baker 2010	Duplicate from Baker 2011.
Beutner 1995	Duplicate from Beutner 1998 and Edwards 1998.
Beutner 1998b	Duplicate from Beutner 1998 and Edwards 1998.
Buck 2002	Not a RCT.
Carey 2004	Not a RCT.
Carrasco 2002	No intervention: use of imiquimod before all intervention groups
Castellsague 2000	Not a RCT.
Chopra 1997	Duplicate from Tyring 1998.
Como 2010	Not a RCT.
Corona 2002	Not a RCT.
Dall'oglio 2012	Not a RCT.
Desai 2006	Not a RCT.
Edwards 1995	Duplicate from Edwards 1998.
Ferenczy 1998	Duplicate from Edwards 1998.
Ferris 2010	Duplicate from Baker 2011.
Fife 2001	Not comparison: all the intervention groups included imiquimod
Garland 2001	Not a RCT.
Garland 2006	Not comparison: all the intervention groups included imiquimod
Gibbs 2006	Not a RCT.
Gollnick 2001	Not a RCT.
Gotovtseva 2008	Not a RCT.
Jaffary 2007	Not a RCT.
Jappe 1998	Not a RCT.
Kwok 2012	Not a RCT.
Lafuma 2003	Not a RCT.
Langley 2010	Not a RCT.
Maw 2002	Not a RCT.
Maw 2004	Not a RCT.
Meltzer 2009	Not a RCT.
Miller 1999a	Not a RCT.
Mistrangelo 2010	No intervention: not imiquimod.
Moore 2001	Not a RCT.
NCT00114023	Not a RCT.
NCT00189293	No intervention: use of imiquimod before all intervention groups
NCT00674739	Duplicate from Baker 2011.
NCT00735462	Duplicate from Baker 2011.
NCT00941811	Not a RCT.
NCT00979550	No intervention: not imiquimod alone.
O'Mahony 2001	Not a RCT.
Owens 1999	Duplicate from Edwards 1998.
Puri 2009	Not a RCT.
Sauder 2003a	Duplicate from Edwards 1998.
Sauder 2003b	No intervention: not imiquimod.
Schöfer 2007	Not a RCT.
Syed 1998	Risk of fraud.
Syed 2000	Risk of fraud.
Syed 2002	Risk of fraud.
Trofatter 1998	Not a RCT.
Trofatter 2002	No comparison: all the intervention groups included imiquimod
Tuncel 2005	No comparison: all the intervention groups included imiquimod
Tyring 1997	Duplicate from Beutner 1998 and Edwards 1998.
Walczak 2009	Not a RCT.

Walczak 2009a	Not a RCT.
Wang 2007	Not a RCT: cross-over design
Weinberg 1997	Not a RCT.
Williams 2003	Not a RCT.
Yan 2006	Not a RCT.

Tabla 3: Characteistics of studies awaiting assessment.

CTRI/2009/091/000055

Methods	RCT
Participants	Patients with AGW, with surface area of warts 10 mm2 or more, healthy adults, > 12 years of age, without treatment during past 4 weeks. 89 patients (71 male and 18 female)
Interventions	Mycobacterium vaccine (maximum up to 0.1 mL in one session). 5%imiquimod cream 3 times a week for 16 weeks. Follow-up period of up to 16 weeks
Outcomes	Complete clearance, adverse events.

Ferenczy 1999

Methods	Two multicenter, randomized, vehicle-controlled, double-blind clinical trials
Participants	Female patients with AGW. 119 female were to imiquimod group, 105 female were to vehicle group
Interventions	Imiquimod 5% or vehicle cream, three times per week for up to 16 weeks or until wart clearance, follow-up period of up to 12 weeks
Outcomes	Complete clearance, partial clearance, adverse events.

Nelson 2014

Methods	Two identical multicenter, randomized, double-blind, placebo controlled studies
Participants	Subjects (12 years old) with 2 to 30 external genital warts and total wart area of 10 mm^2. 981 subjects were enrolled (470 subjects Study 1 and 511 subjects Study 2)
Interventions	Imiquimod 3.75%, imiquimod 2.5%, or vehicle cream (2:2:1) once daily until complete clearance or a maximum of 8 weeks, follow-up period of up to 12 weeks
Outcomes	Complete clearance, partial clearance, time to clearance, visual assessment of local skin reaction

C. Appendix 3: Data and analyses[9]

Comparison 1: Imiquimod versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete regression after treatment	6	1294	Risk Ratio (M-H, Random, 95% CI)	4.03 [2.03, 7.99]
2 Partial regression after treatment	6	1082	Risk Ratio (M-H, Fixed, 95% CI)	2.56 [2.05, 3.20]
3 Recurrence during follow-up from 0 to 6 months	3	270	Risk Ratio (M-H, Fixed, 95% CI)	2.76 [0.70, 10.91]
4 Appearance of new warts during treatment	3	671	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.58, 1.00]
5 Pain during therapy	2	804	Risk Ratio (M-H, Fixed, 95% CI)	11.84 [3.36, 41.63]
6 Any local reactions during therapy	5	1225	Risk Ratio (M-H, Random, 95% CI)	1.73 [1.18, 2.53]
7 Any systemic reactions during therapy	2	313	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.63, 1.32]

[9] This document has been published elsewhere as form of the review entitled Imiquimod for anogenital warts in non-immunocompromised adults, published in The Cochrane Library 2014, Issue 11; available on: http://www.thecochranelibrary.com

Comparison 2: Imiquimod versus any other patient-applied treatment.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete regression after treatment	2	105	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.80, 1.48]
2 Partial regression after treatment	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.40, 1.47]
3 Recurrence during follow-up from 0 to 6 months	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.21, 1.11]
4 Any local reactions during therapy	2	105	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.00, 1.54]
5 Any systemic reactions during therapy	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.3 [0.09, 0.98]

Comparison 3: Imiquimod versus any other provider-administered treatment.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete regression after treatment	2	335	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.56, 1.28]
2 Recurrence during follow-up from 0 to 6 months	1	192	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.10, 0.56]
3 Recurrence during follow-up from 6 to 12 months	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.40, 1.25]
4 Pain during therapy	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.17, 0.54]
5 Any local reactions during therapy	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.40, 0.74]

Comparison 4: Imiquimod versus placebo (outcome: complete regression after treatment).

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Concentration of imiquimod	6	1294	Risk Ratio (M-H, Random, 95% CI)	3.84 [2.12, 6.93]
1.1 Less than 5%	3	823	Risk Ratio (M-H, Random, 95% CI)	2.35 [1.54, 3.59]
1.2 5% or more	5	471	Risk Ratio (M-H, Random, 95% CI)	5.82 [2.26, 14.98]

Comparison 5: Imiquimod versus placebo (outcome: complete regression after treatment).

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of therapy	6	1294	Risk Ratio (M-H, Random, 95% CI)	4.03 [2.03, 7.99]
1.1 12 or less weeks	3	685	Risk Ratio (M-H, Random, 95% CI)	5.93 [1.15, 30.61]
1.2 More than 12 weeks	3	609	Risk Ratio (M-H, Random, 95% CI)	3.91 [1.40, 10.97]

Comparison 6: Imiquimod versus placebo (outcome: complete regression after treatment).

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Times per week	6	1294	Risk Ratio (M-H, Random, 95% CI)	4.03 [2.03, 7.99]
1.1 Once daily	2	813	Risk Ratio (M-H, Random, 95% CI)	4.57 [0.95, 21.93]
1.2 Any other frequency per week	4	481	Risk Ratio (M-H, Random, 95% CI)	4.15 [1.42, 12.12]

Comparison 7: Imiquimod versus placebo (outcome: complete regression after treatment).

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesion site	2	701	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [1.64, 2.88]
1.1 Perineal skin	2	210	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [1.43, 3.96]
1.2 Perianal skin	2	188	Risk Ratio (M-H, Fixed, 95% CI)	2.70 [1.57, 4.64]
1.3 Other site	2	303	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.10, 2.62]

Comparison 8: Imiquimod versus placebo (outcome: complete regression after treatment).

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sex of the patient	4	1167	Risk Ratio (M-H, Fixed, 95% CI)	3.38 [2.42, 4.74]
1.1 Female	4	803	Risk Ratio (M-H, Fixed, 95% CI)	2.90 [2.02, 4.17]
1.2 Male	3	364	Risk Ratio (M-H, Fixed, 95% CI)	6.54 [2.60, 16.43]

Comparison 9: Imiquimod versus placebo (outcome: partial regression after treatment).

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Concentration of imiquimod	6	1082	Risk Ratio (M-H, Random, 95% CI)	2.51 [1.83, 3.45]
1.1 Less than 5%	3	659	Risk Ratio (M-H, Random, 95% CI)	1.89 [1.14, 3.13]
1.2 5% or more	5	423	Risk Ratio (M-H, Random, 95% CI)	3.26 [2.35, 4.54]

Comparison 10: Imiquimod versus placebo (outcome: partial regression after treatment).

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of therapy	6	1082	Risk Ratio (M-H, Random, 95% CI)	2.95 [2.02, 4.31]
1.1 12 or less weeks	3	529	Risk Ratio (M-H, Random, 95% CI)	4.30 [1.74, 10.64]
1.2 More than 12 weeks	3	553	Risk Ratio (M-H, Random, 95% CI)	2.31 [1.78, 3.01]

Comparison 11: Imiquimod versus placebo (outcome: partial regression after treatment).

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Times per week	6	1082	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [2.05, 3.21]
1.1 Once daily	2	614	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [2.05, 3.86]
1.2 Any other frequency per week	4	468	Risk Ratio (M-H, Fixed, 95% CI)	2.30 [1.68, 3.15]

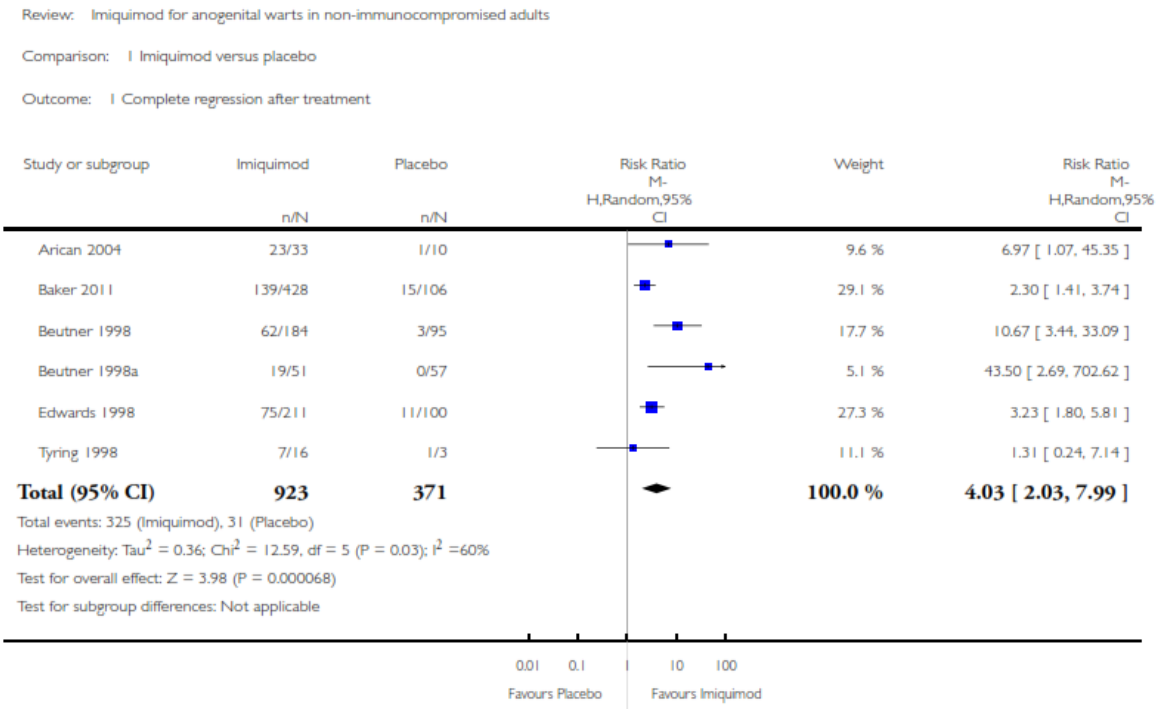
Comparison 12: Imiquimod versus placebo (outcome: partial regression after treatment).

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lesion site	1	42	Risk Ratio (M-H, Fixed, 95% CI)	2.60 [0.56, 12.08]
1.1 Perineal skin	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.84 [0.45, 18.09]
1.2 Perianal skin	1	14	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Other site	1	3	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.14, 28.42]

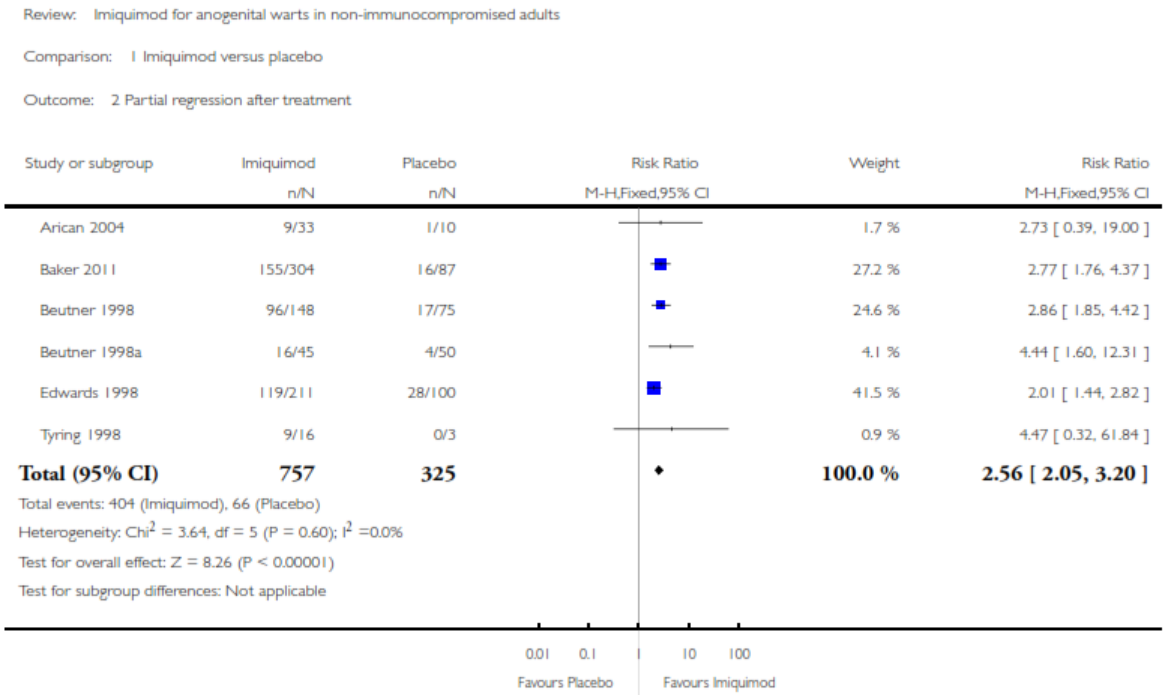
Comparison 13: Imiquimod versus placebo (outcome: partial regression after treatment).

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sex of the patient	3	745	Risk Ratio (M-H, Random, 95% CI)	2.14 [1.39, 3.29]
1.1 Female	3	535	Risk Ratio (M-H, Random, 95% CI)	1.88 [0.93, 3.81]
1.2 Male	2	210	Risk Ratio (M-H, Random, 95% CI)	2.29 [1.38, 3.81]

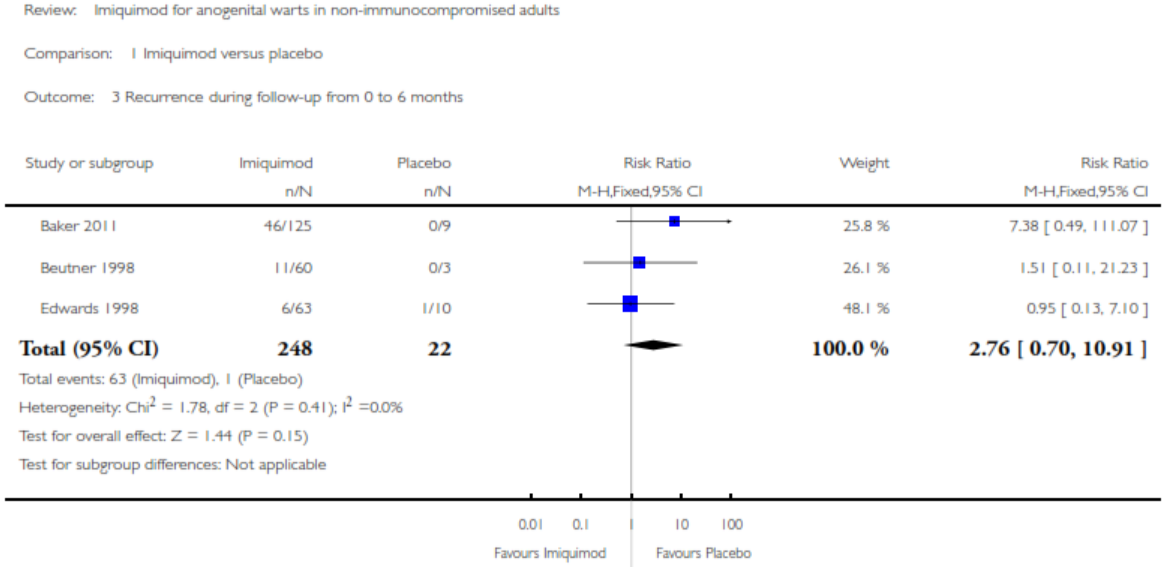
Analysis 14.1: Comparison 1 Imiquimod versus placebo, Outcome 1 Complete regression after treatment.



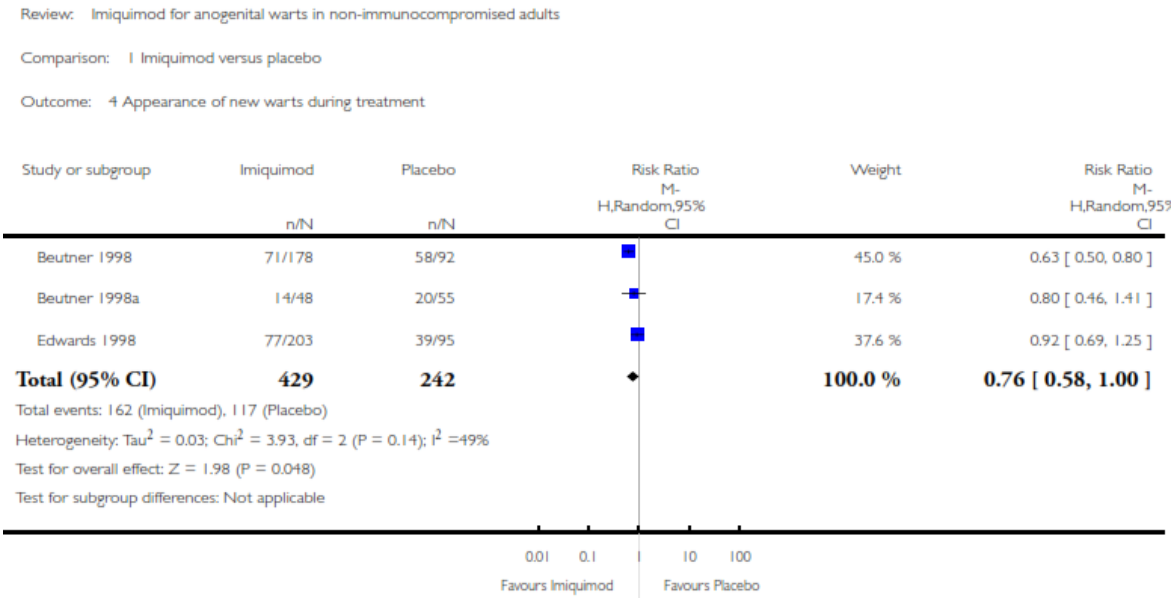
Analysis 15.2: Comparison 1 Imiquimod versus placebo, Outcome 2 Partial regression after treatment.



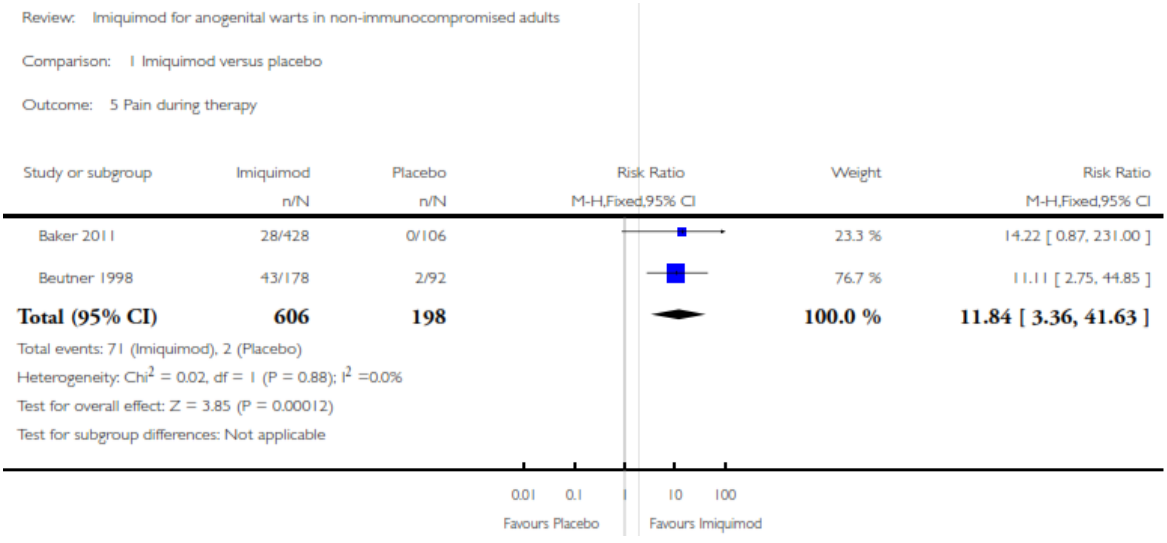
Analysis 16.17: Comparison 1 Imiquimod versus placebo, Outcome 3 Recurrence during follow-up from 0 to 6 months.



Analysis 18.19: Comparison 1 Imiquimod versus placebo, Outcome 4 Appearance of new warts during treatment.



Analysis 20.21: Comparison 1 Imiquimod versus placebo, Outcome 5 Pain during therapy.

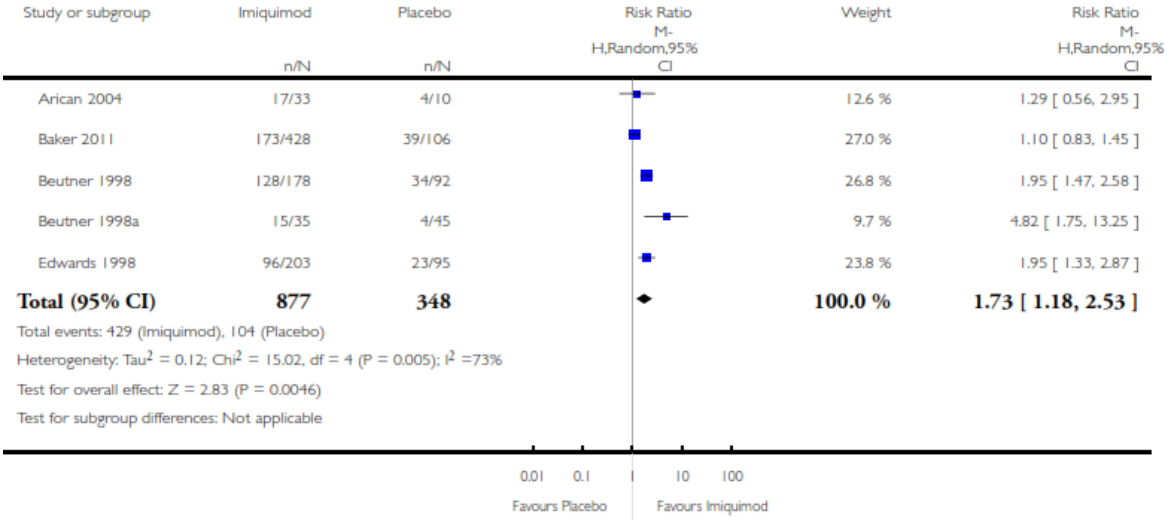


Analysis 22.23: Comparison 1 Imiquimod versus placebo, Outcome 6 Any local reactions during therapy.

Review: Imiquimod for anogenital warts in non-immunocompromised adults

Comparison: 1 Imiquimod versus placebo

Outcome: 6 Any local reactions during therapy

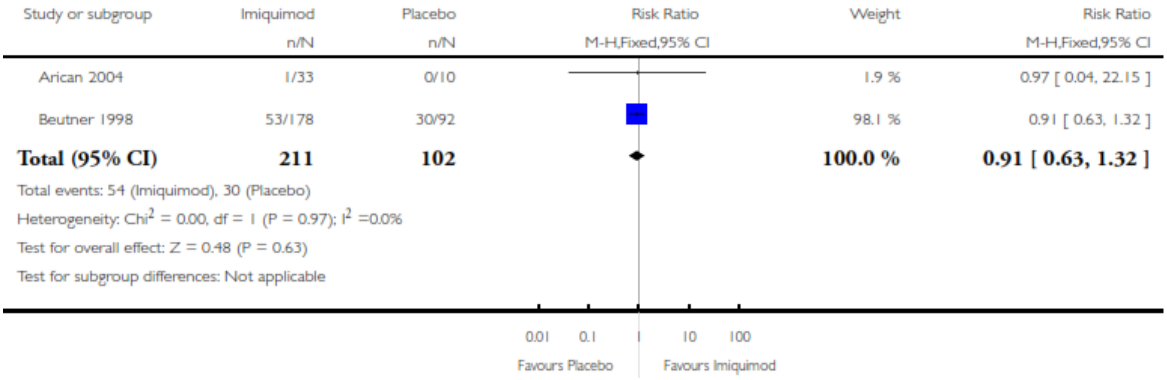


Analysis 24.25: Comparison 1 Imiquimod versus placebo, Outcome 7 Any systemic reactions during therapy.

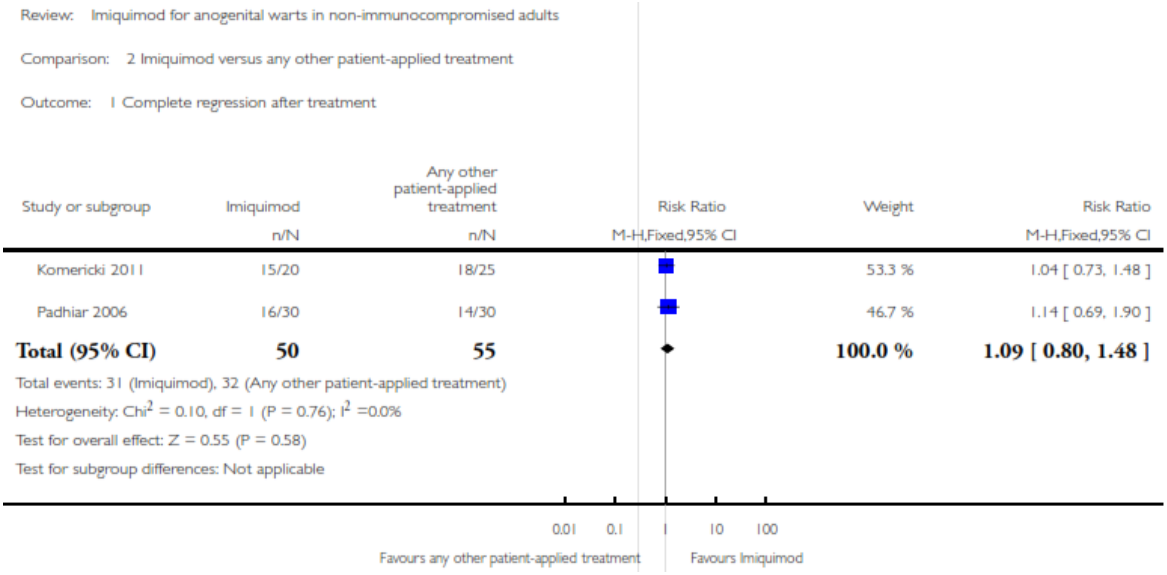
Review: Imiquimod for anogenital warts in non-immunocompromised adults

Comparison: 1 Imiquimod versus placebo

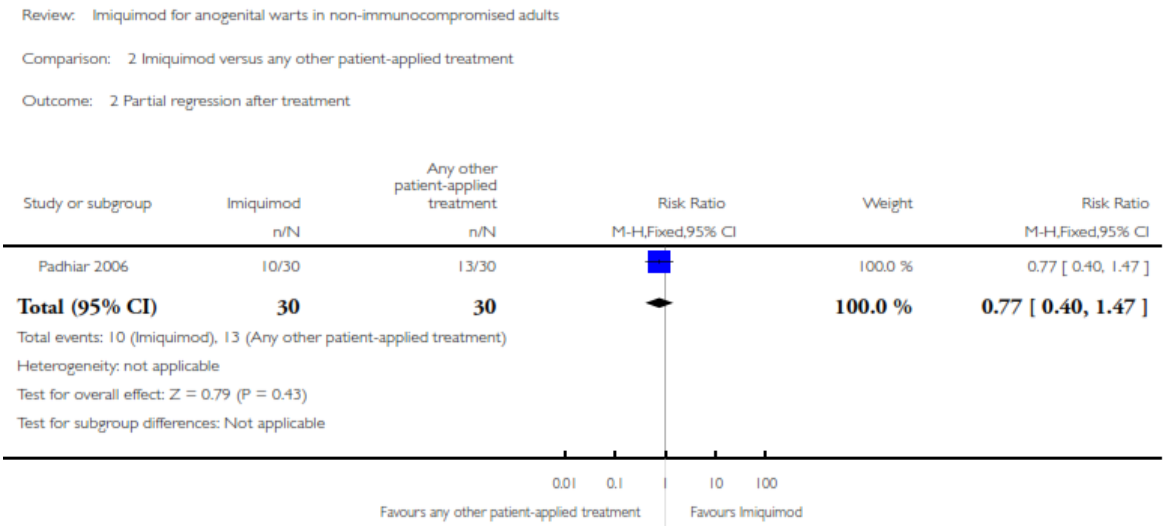
Outcome: 7 Any systemic reactions during therapy



Analysis 26.1: Comparison 2 Imiquimod versus any other patient-applied treatment, Outcome 1 Complete regression after treatment.



Analysis 27.2: Comparison 2 Imiquimod versus any other patient-applied treatment, Outcome 2 Partial regression after treatment.

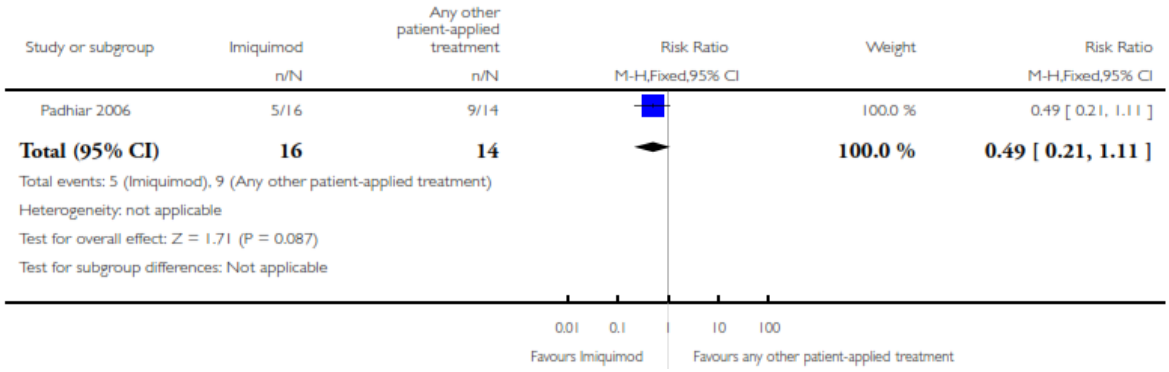


Analysis 28.3: Comparison 2 Imiquimod versus any other patient-applied treatment, Outcome 3 Recurrence during follow-up from 0 to 6 months.

Review: Imiquimod for anogenital warts in non-immunocompromised adults

Comparison: 2 Imiquimod versus any other patient-applied treatment

Outcome: 3 Recurrence during follow-up from 0 to 6 months

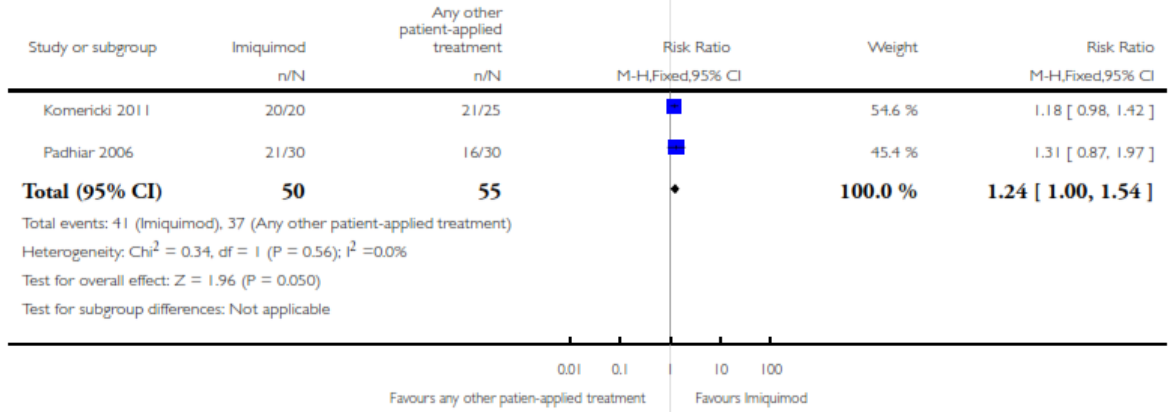


Analysis 29.4: Comparison 2 Imiquimod versus any other patient-applied treatment, Outcome 4 Any local reactions during therapy.

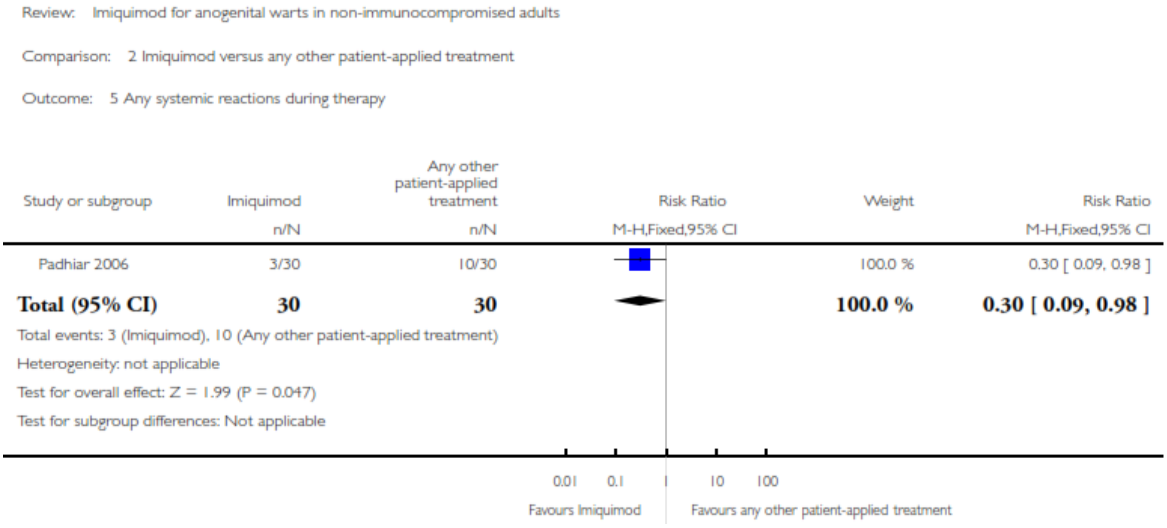
Review: Imiquimod for anogenital warts in non-immunocompromised adults

Comparison: 2 Imiquimod versus any other patient-applied treatment

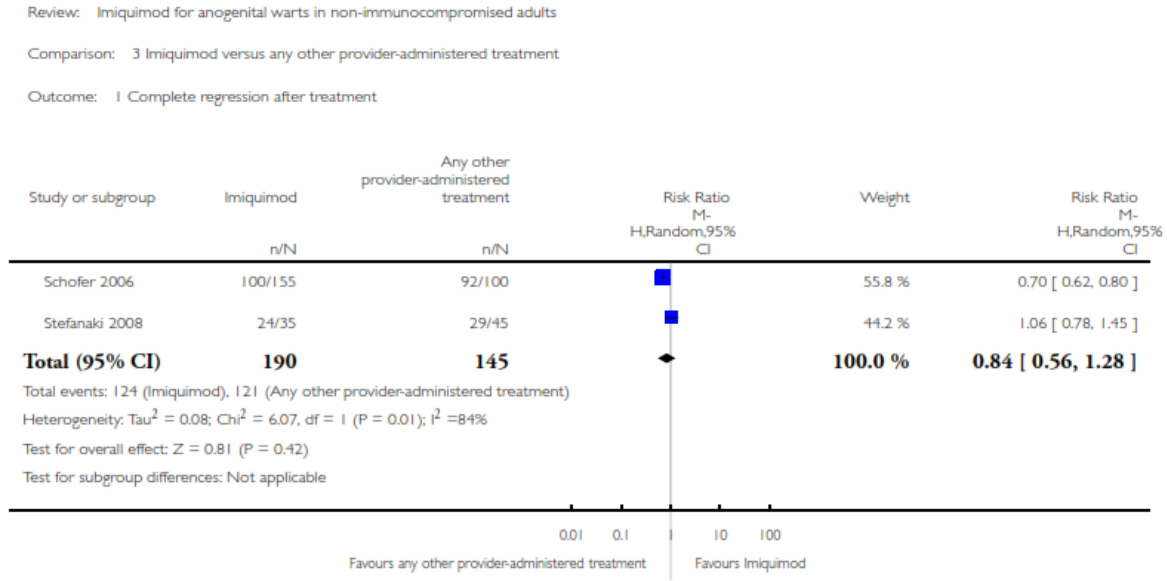
Outcome: 4 Any local reactions during therapy



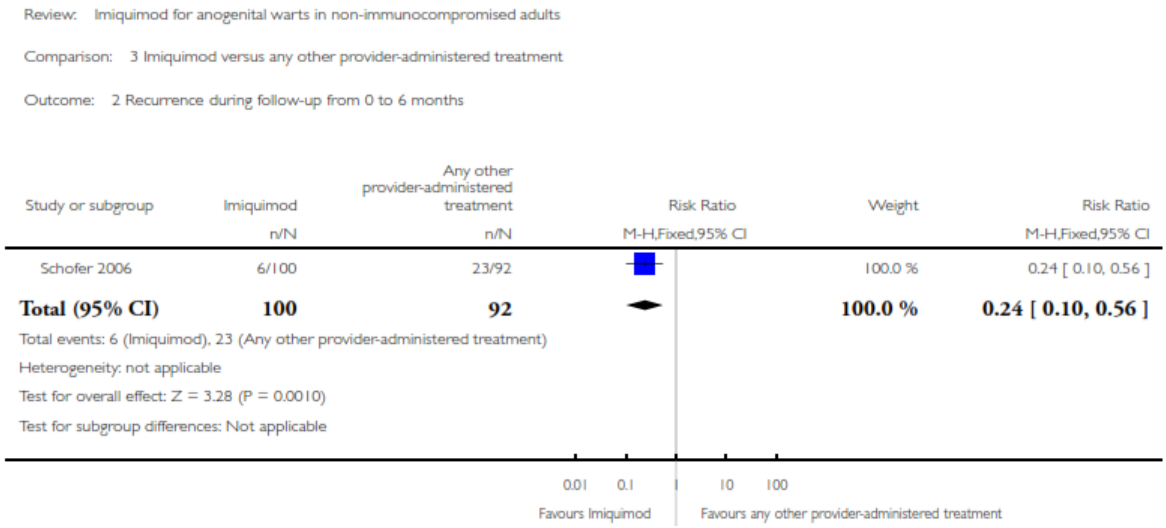
Analysis 30.5: Comparison 2 Imiquimod versus any other patient-applied treatment, Outcome 5 Any systemic reactions during therapy.



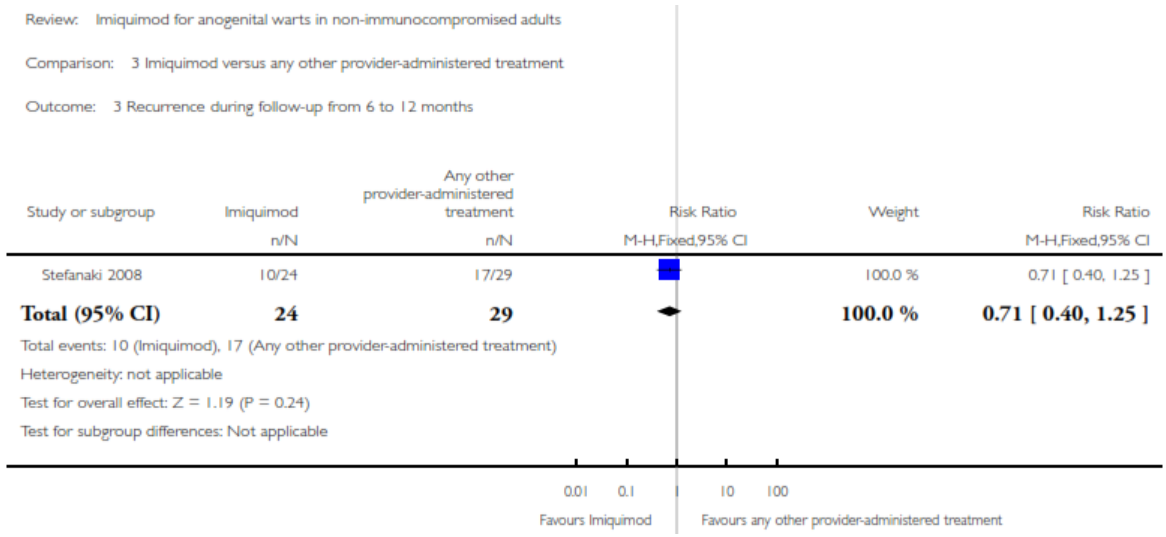
Analysis 31: Comparison 3 Imiquimod versus any other provider-administered treatment, Outcome 1 Complete regression after treatment.



Analysis 32: Comparison 3 Imiquimod versus any other provider-administered treatment, Outcome 2 Recurrence during follow-up from 0 to 6 months.



Analysis 33: Comparison 3 Imiquimod versus any other provider-administered treatment, Outcome 3 Recurrence during follow-up from 6 to 12 months.



Analysis 34: Comparison 3 Imiquimod versus any other provider-administered treatment, Outcome 4 Pain during therapy.

Review: Imiquimod for anogenital warts in non-immunocompromised adults

Comparison: 3 Imiquimod versus any other provider-administered treatment

Outcome: 4 Pain during therapy

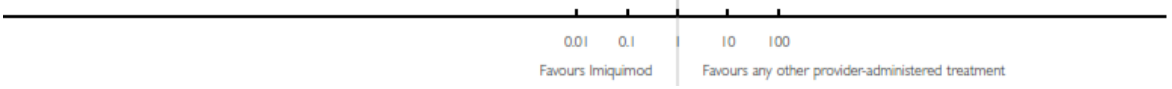
Study or subgroup	Imiquimod n/N	Any other provider-administered treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Stefanaki 2008	9/35	38/45		100.0 %	0.30 [0.17, 0.54]
Total (95% CI)	**35**	**45**		**100.0 %**	**0.30 [0.17, 0.54]**

Total events: 9 (Imiquimod), 38 (Any other provider-administered treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 4.04 (P = 0.000054)

Test for subgroup differences: Not applicable



Analysis 35: Comparison 3 Imiquimod versus any other provider-administered treatment, Outcome 5 Any local reactions during therapy.

Review: Imiquimod for anogenital warts in non-immunocompromised adults

Comparison: 3 Imiquimod versus any other provider-administered treatment

Outcome: 5 Any local reactions during therapy

Study or subgroup	Imiquimod n/N	Any other provider-administered treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Stefanaki 2008	19/35	45/45		100.0 %	0.55 [0.40, 0.74]
Total (95% CI)	**35**	**45**		**100.0 %**	**0.55 [0.40, 0.74]**

Total events: 19 (Imiquimod), 45 (Any other provider-administered treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 3.91 (P = 0.000093)

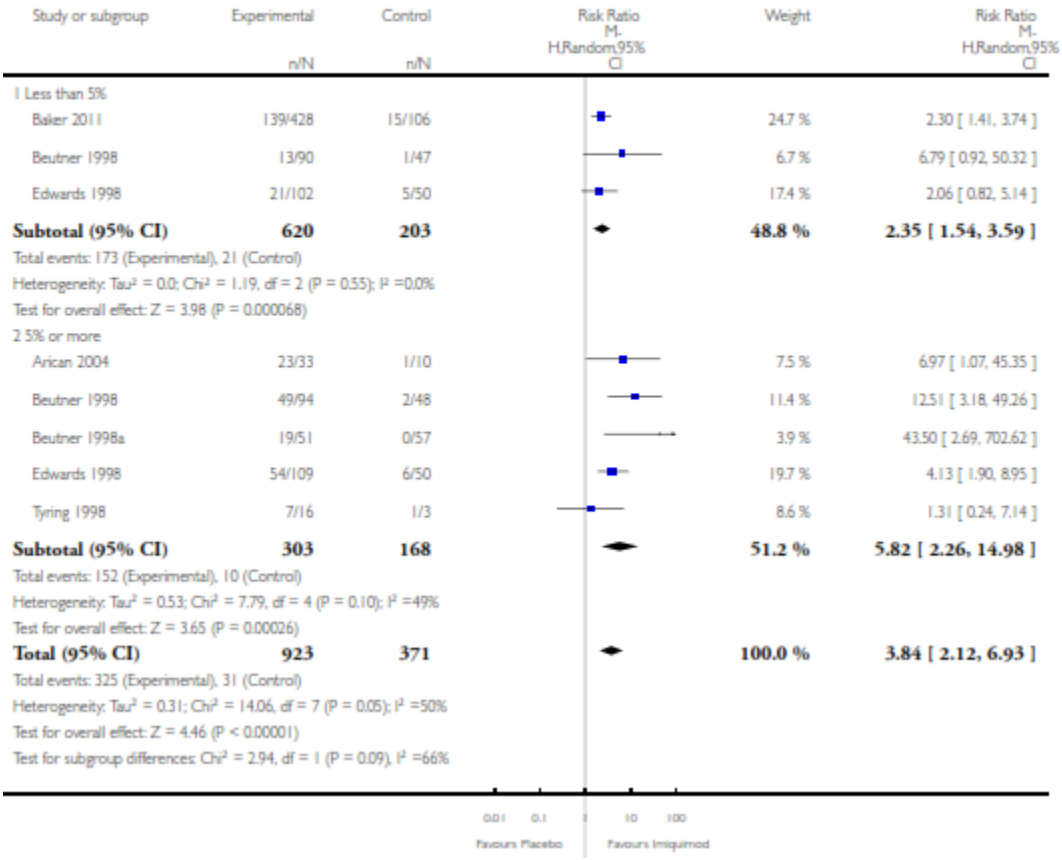
Test for subgroup differences: Not applicable

Analysis 36.1: Comparison 4 Imiquimod versus placebo (outcome: complete regression after treatment), Outcome 1 Concentration of imiquimod.

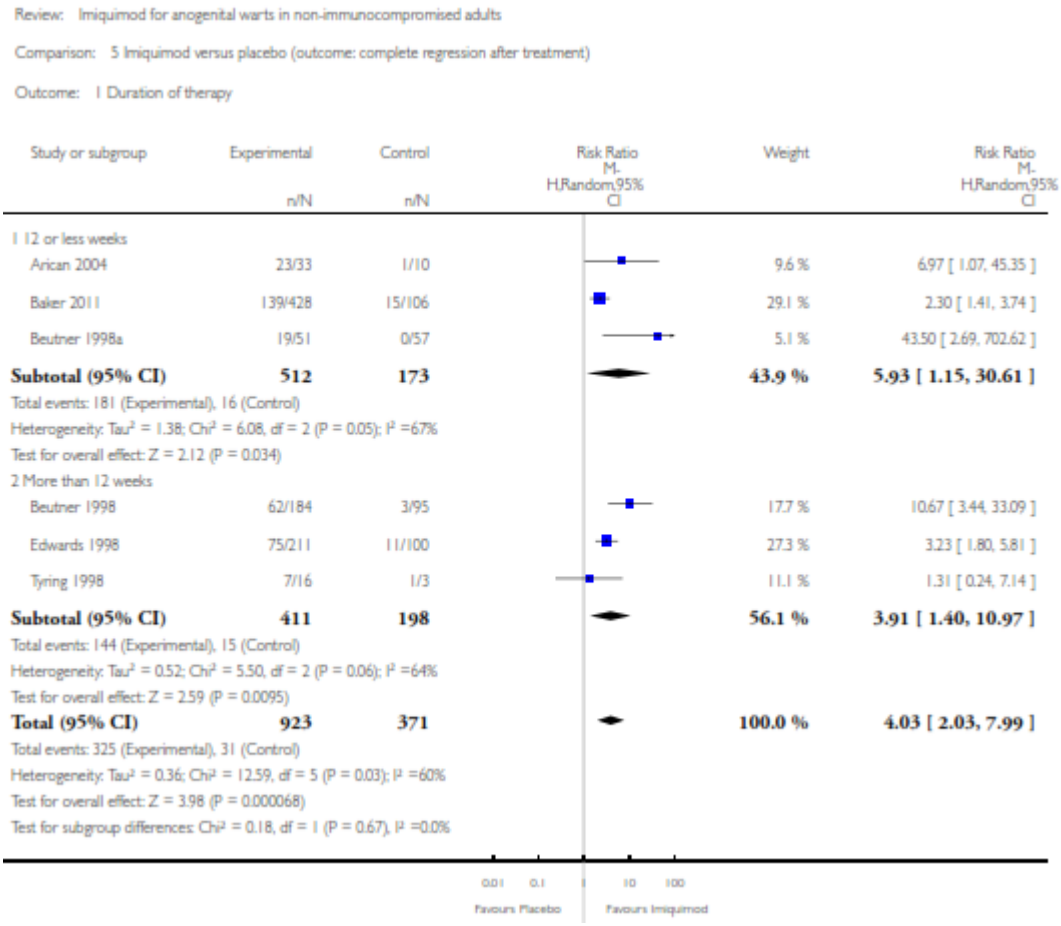
Review: Imiquimod for anogenital warts in non-immunocompromised adults

Comparison: 4 Imiquimod versus placebo (outcome: complete regression after treatment)

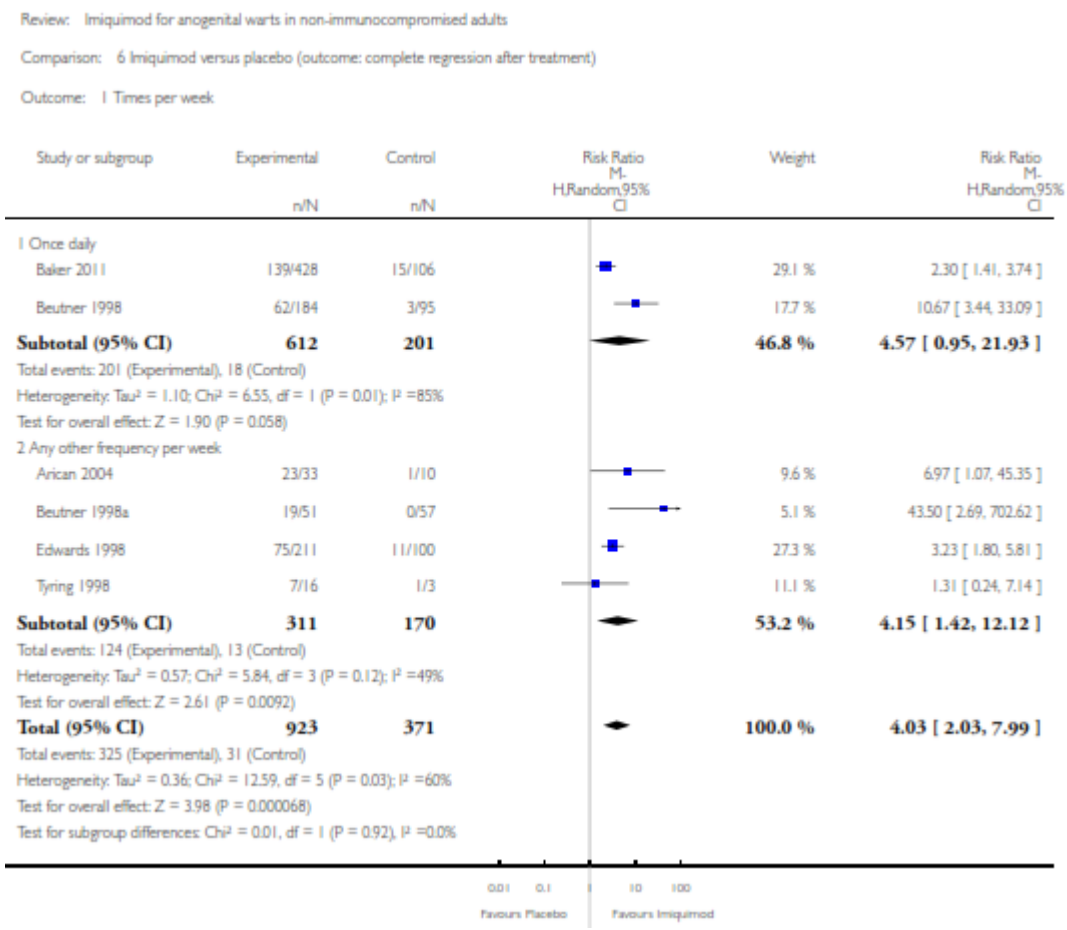
Outcome: 1 Concentration of imiquimod



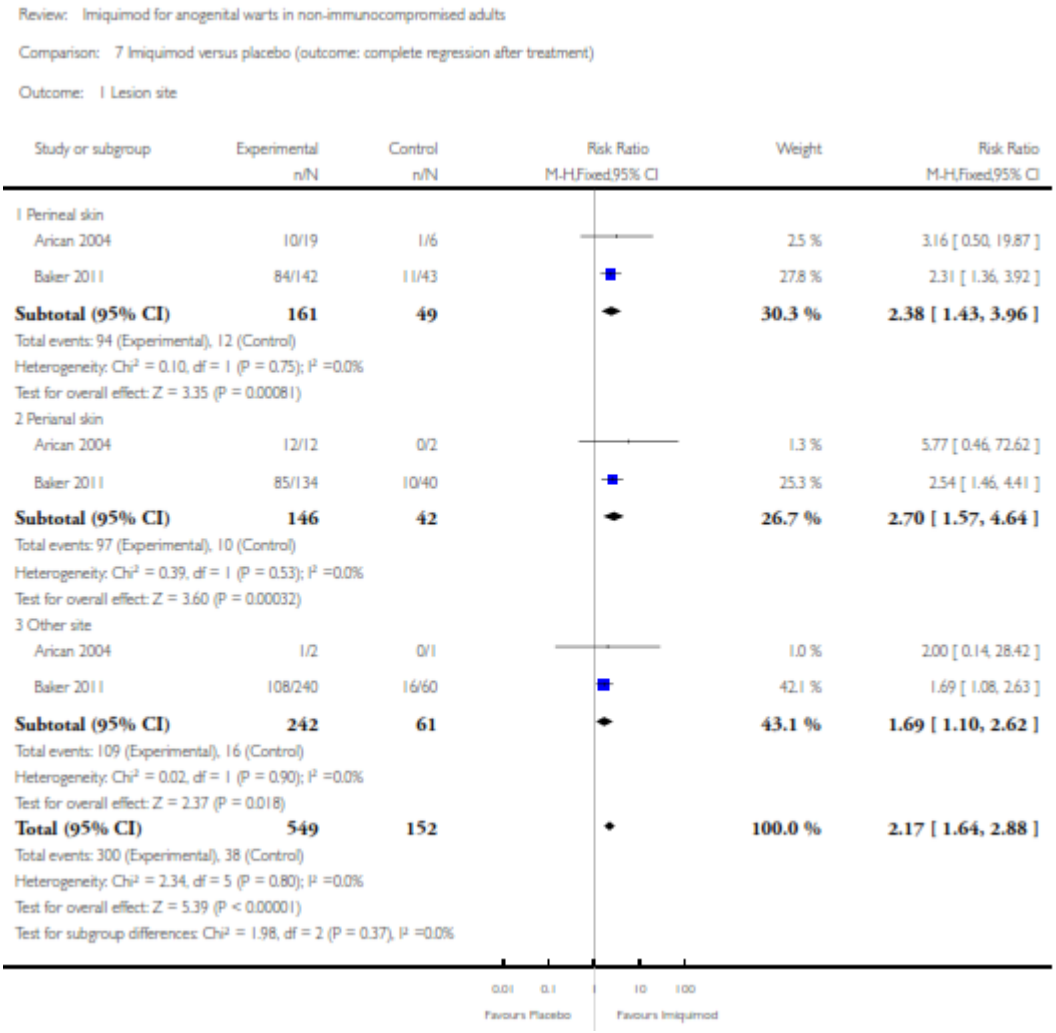
Analysis 37: Comparison 5 Imiquimod versus placebo (outcome: complete regression after treatment), Outcome 1 Duration of therapy.



Analysis 38: Comparison 6 Imiquimod versus placebo (outcome: complete regression after treatment), Outcome 1 Times per week.



Analysis 39: Comparison 7 Imiquimod versus placebo (outcome: complete regression after treatment), Outcome 1 Lesion site.



Analysis 40: Comparison 8 Imiquimod versus placebo (outcome: complete regression after treatment), Outcome 1 Sex of the patient.

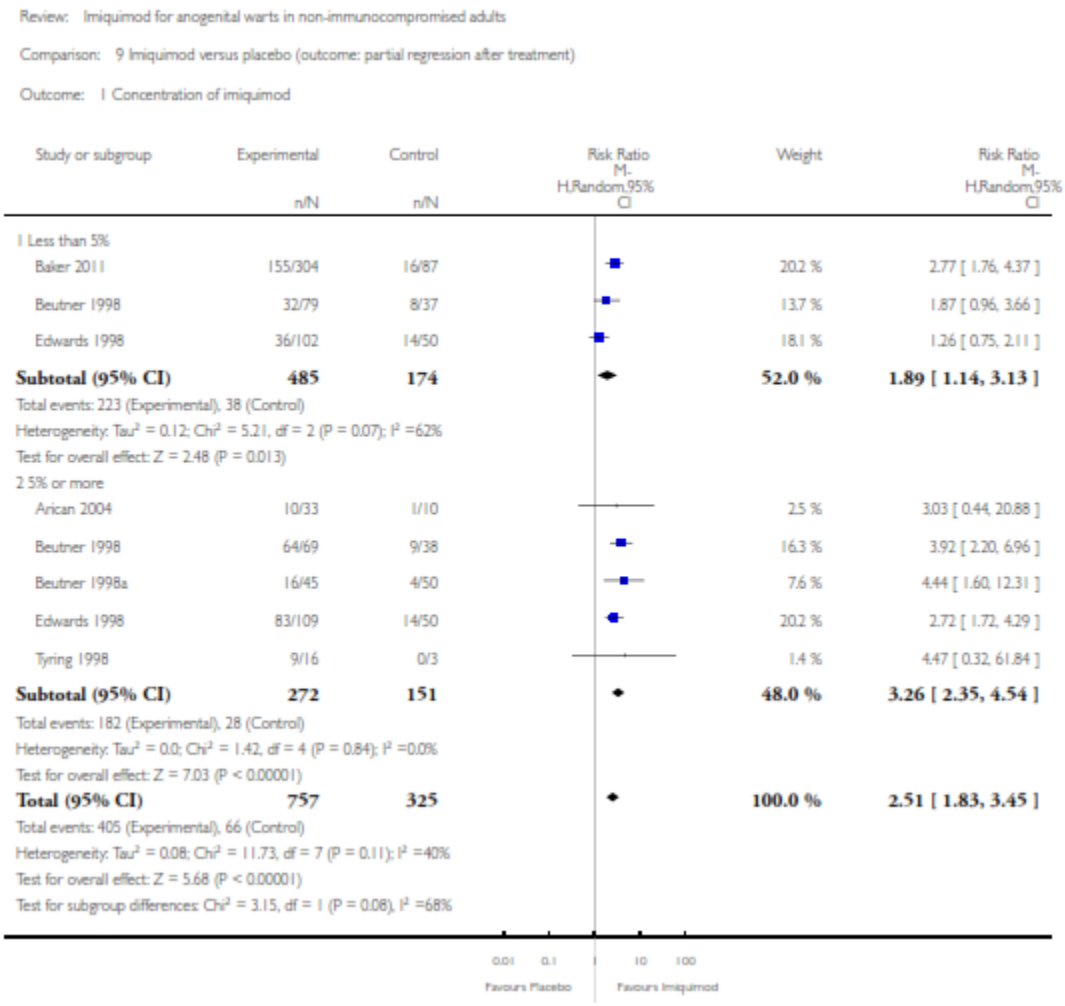
Review: Imiquimod for anogenital warts in non-immunocompromised adults

Comparison: 8 Imiquimod versus placebo (outcome: complete regression after treatment)

Outcome: 1 Sex of the patient

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Female					
Arican 2004	11/11	0/2		1.7 %	5.75 [0.46, 72.40]
Baker 2011	139/428	15/106		52.2 %	2.30 [1.41, 3.74]
Beutner 1998	38/83	3/42		8.6 %	6.41 [2.10, 19.55]
Edwards 1998	50/91	8/40		24.1 %	2.75 [1.44, 5.25]
Subtotal (95% CI)	**613**	**190**		**86.7 %**	**2.90 [2.02, 4.17]**
Total events: 238 (Experimental), 26 (Control)					
Heterogeneity: Chi^2 = 3.13, df = 3 (P = 0.37); I^2 =4%					
Test for overall effect: Z = 5.75 (P < 0.00001)					
2 Male					
Arican 2004	12/22	1/8		3.2 %	4.36 [0.67, 28.39]
Beutner 1998	24/101	0/53		1.4 %	25.94 [1.61, 418.34]
Edwards 1998	25/120	3/60		8.7 %	4.17 [1.31, 13.25]
Subtotal (95% CI)	**243**	**121**		**13.3 %**	**6.54 [2.60, 16.43]**
Total events: 61 (Experimental), 4 (Control)					
Heterogeneity: Chi^2 = 1.71, df = 2 (P = 0.43); I^2 =0.0%					
Test for overall effect: Z = 4.00 (P = 0.000064)					
Total (95% CI)	**856**	**311**		**100.0 %**	**3.38 [2.42, 4.74]**
Total events: 299 (Experimental), 30 (Control)					
Heterogeneity: Chi^2 = 6.51, df = 6 (P = 0.37); I^2 =8%					
Test for overall effect: Z = 7.09 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.59, df = 1 (P = 0.11), I^2 =61%					

Analysis 41: Comparison 9 Imiquimod versus placebo (outcome: partial regression after treatment), Outcome 1 Concentration of imiquimod.

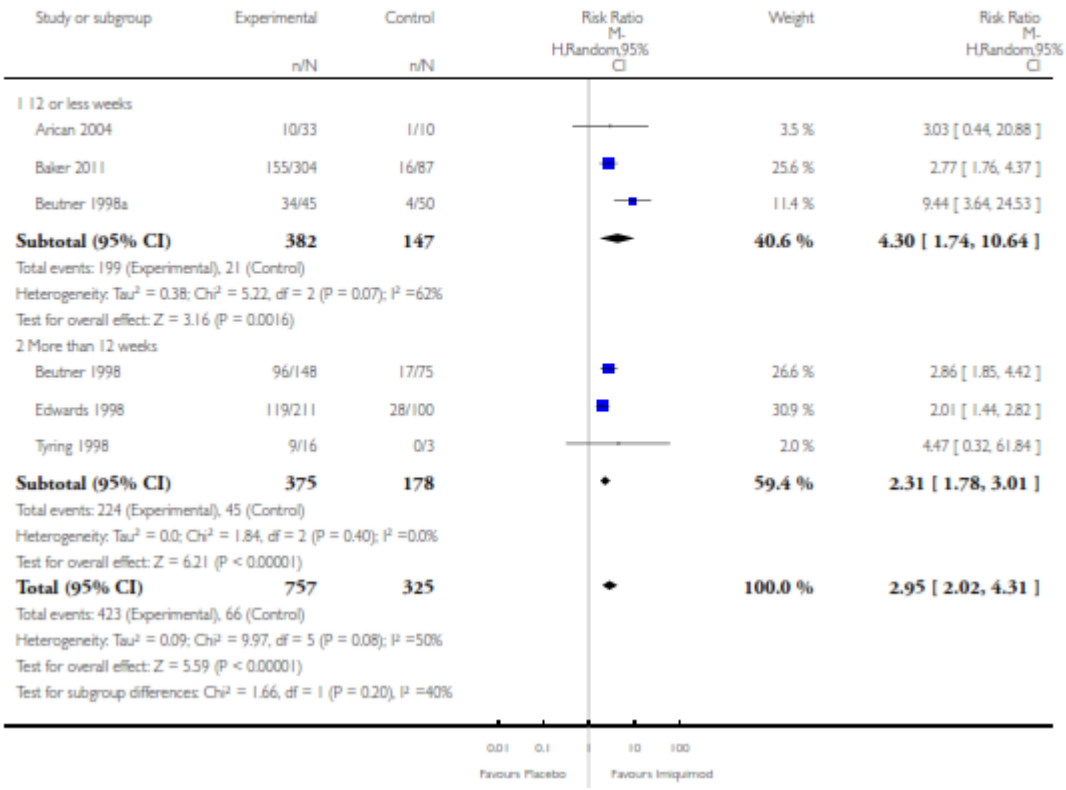


Analysis 42: Comparison 10 Imiquimod versus placebo (outcome: partial regression after treatment), Outcome 1 Duration of therapy.

Review: Imiquimod for anogenital warts in non-immunocompromised adults

Comparison: 10 Imiquimod versus placebo (outcome: partial regression after treatment)

Outcome: 1 Duration of therapy



Analysis 43: Comparison 11 Imiquimod versus placebo (outcome: partial regression after treatment), Outcome 1 Times per week.

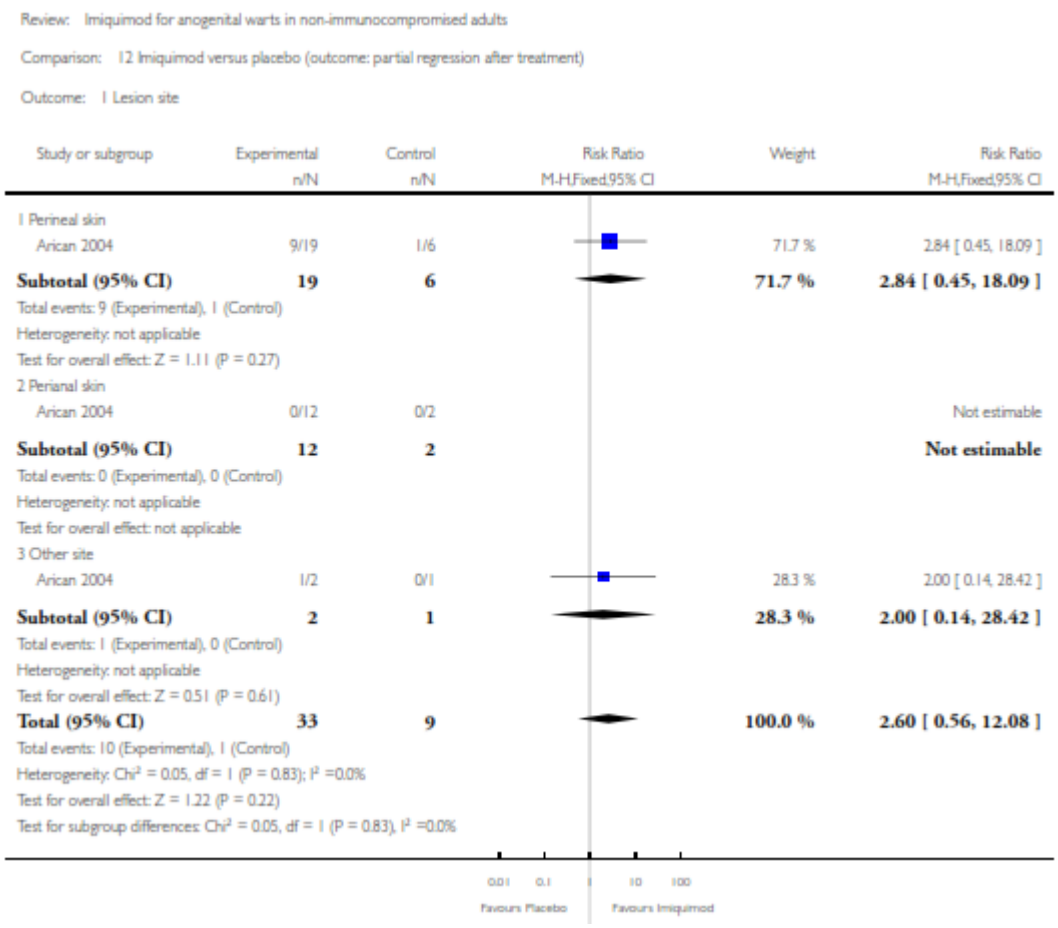
Review: Imiquimod for anogenital warts in non-immunocompromised adults

Comparison: 11 Imiquimod versus placebo (outcome: partial regression after treatment)

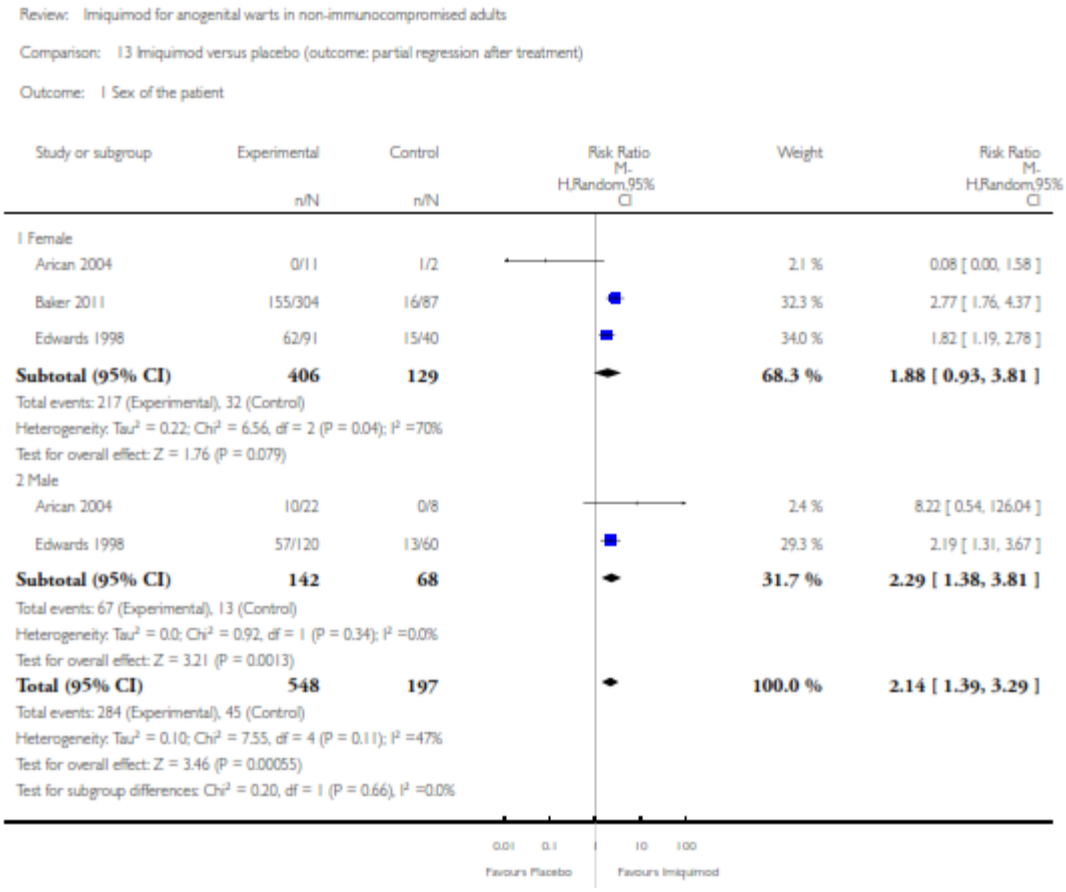
Outcome: 1 Times per week

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Once daily					
Baker 2011	155/304	16/87		27.2 %	2.77 [1.76, 4.37]
Beutner 1998	96/148	17/75		24.6 %	2.86 [1.85, 4.42]
Subtotal (95% CI)	**452**	**162**		**51.8 %**	**2.81 [2.05, 3.86]**
Total events: 251 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 6.42 (P < 0.00001)					
2 Any other frequency per week					
Arican 2004	10/33	1/10		1.7 %	3.03 [0.44, 20.88]
Beutner 1998a	16/45	4/50		4.1 %	4.44 [1.60, 12.31]
Edwards 1998	119/211	28/100		41.5 %	2.01 [1.44, 2.82]
Tyring 1998	9/16	0/3		0.9 %	4.47 [0.32, 61.84]
Subtotal (95% CI)	**305**	**163**		**48.2 %**	**2.30 [1.68, 3.15]**
Total events: 154 (Experimental), 33 (Control)					
Heterogeneity: Chi^2 = 2.53, df = 3 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 5.21 (P < 0.00001)					
Total (95% CI)	**757**	**325**		**100.0 %**	**2.57 [2.05, 3.21]**
Total events: 405 (Experimental), 66 (Control)					
Heterogeneity: Chi^2 = 3.67, df = 5 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 8.28 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.78, df = 1 (P = 0.38), I^2 =0.0%					

Analysis 44.1: Comparison 12 Imiquimod versus placebo (outcome: partial regression after treatment), Outcome 1 Lesion site.



Analysis 45.1: Comparison 13 Imiquimod versus placebo (outcome: partial regression after treatment), Outcome 1 Sex of the patient.



D. Appendix 4: Electronic search strategies[10]

MEDLINE and CENTRAL (Ovid platform)

1 exp Condylomata Acuminata/
2 condyl$.tw.
3 acuminat$.tw.
4 accuminat$.tw.
5 exp Warts/
6 wart$.tw.
7 verruca$.tw.
8 papillomavirus$.tw.
9 (papilloma adj5 virus).tw.
10 hpv.tw.
11 or/1-10
12 imiquimod.tw.
13 randomised controlled trial.pt.
14 controlled clinical trial.pt.
15 randomized.ab.
16 placebo.ab.
17 clinical trials as topic.sh.
18 randomly.ab.
19 trial.ti.
20 or/13-19
21 exp animals/ not humans.sh.
22 20 not 21
23 11 and 12 and 22
Note: the CENTRAL search strategy does not include the terms #13 to #22.

[10] This document has been published elsewhere as form of the review entitled Imiquimod for anogenital warts in non-immunocompromised adults, published in The Cochrane Library 2014, Issue 11; available on: http://www.thecochranelibrary.com

EMBASE.com

1 ’condyloma acuminatum’/exp
2 condyl*:ab,ti
3 acuminat*:ab,ti
4 accuminat*:ab,ti
5 ’condyloma latum’/exp
6 ’verruca vulgaris’/exp
7 verruca*:ab,ti
8 wart*:ab,ti
9 ’wart virus’/exp
10 hpv:ab,ti
11 (papilloma NEAR/5 virus):ab,ti
12 papillomavirus*:ab,ti
13 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
14 ’imiquimod’/exp
15 imiquimod:ab,ti
16 14 OR 15
17 ’randomised controlled trial’/exp
18 ’single blind procedure’/exp
19 ’double blind procedure’/exp
20 ’crossover procedure’/exp
21 17 OR 18 OR 19 OR 20
22 random*:ab,ti
23 placebo*:ab,ti
24 allocat*:ab,ti
25 crossover*:ab,ti
26 ’cross over’:ab,ti
27 trial:ti
28 (doubl* NEXT/1 blind*):ab,ti
29 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28
30 21 OR 29
31 ’animal’/de
32 ’animal experiment’/de
33 ’nonhuman’/de
34 31 OR 32 OR 33
35 ’human’/de
36 34 AND 35
37 34 NOT 36
38 30 NOT 37
39 13 AND 16 AND 38 AND [embase]/lim

Cochrane Sexually Transmitted Infections Group Specialized Register

Using the terms “imiquimod” and “wart” in title, abstract and keywords.

Other sources search strategies

Web of Science

Topic CONTAINS: ((“condylomata acuminata”) OR (condyl* OR acuminat* OR accuminat*) OR (“warts”) OR (wart* OR verruca*) OR (papillomavirus* OR hpv) OR (papilloma NEAR/5 virus)) AND (imiquimod)

Clinical Trials

Search terms: Imiquimod

International Clinical Trials Registry Platform

Keywords CONTAINS: Imiquimod

Open SIGLE

Keywords CONTAINS: (condyloma) OR (warts) OR (veruucas) OR (acuminate) OR (accuminata) OR (acuminatum) OR (papillomavirus) OR (papilloma NEAR/5 virus) OR (hpv) AND (imiquimod) discipline:(06E - Medicine)

E. Appendix 5: Authorship[11]

Contributions of authors

Grillo-Ardila CF, Angel-Müller E and Salazar-Díaz LC conducted the titles selection, assessed trials quality, extracted data, carried out data analysis and wrote the first draft of the review and made subsequent amendments. Gaitan HG assessed trial quality, performed data analyses, commented on and revised the systematic review draft. AI Ruiz-Parra AI carried out data analyses, commented on and revised the first manuscript draft. Lethaby A commented and revised the manuscript draft.

Declarations of interest

None of the review authors had studies that were included in this Cochrane Review. Salazar-Díaz LC received financial support from the Colombian Department for Science, Technology and Innovation Colciencias as part of a program named “Young researchers” (Grant No: 566/2012). This review was developed independently by the review author team and this entity was not part of the development process.

Sources of support

Internal sources

- No sources of support supplied

External sources

- National University of Colombia, Colombia.

[11] This document has been published elsewhere as form of the review entitled Imiquimod for anogenital warts in non-immunocompromised adults, published in The Cochrane Library 2014, Issue 11; available on: http://www.thecochranelibrary.com

References[12]

References to studies included in this review

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Beutner 1998 *{published data only}*
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Beutner 1998a *{published data only}*
Beutner KR, Spruance SL, Hougham AJ, Fox TL, Owens ML, Douglas JM Jr. Treatment of genital warts with an immune-response modifier (imiquimod). *Journal of the American Academy of Dermatology* 1998;**38**(2 Pt 1):230–9.
Edwards 1998 *{published data only}*
Edwards L, Ferenczy A, Eron L, Baker D, Owens ML, Fox TL, et al.Self-administered topical 5% imiquimod cream for external anogenital warts. *Archives of Dermatology* 1998; **134**(1):25–30.
Komericki 2011 *{published data only}*

[12] This document has been published elsewhere as form of the review entitled Imiquimod for anogenital warts in non-immunocompromised adults, published in The Cochrane Library 2014, Issue 11; available on: http://www.thecochranelibrary.com

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