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Does Bacillus Calmette-Guérin vaccine prevent herpes simplex virus recurrences? A systematic review

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SUMMARY

Recurrent infections with herpes simplex virus (HSV) in the orofacial (cold sores), ocular or genital region are common and sometimes disabling, calling for an effective preventive intervention. The bacillus Calmette-Guérin (BCG) vaccine has beneficial off-target effects that might impact recurrence of HSV infections. In this systematic review, Medline, EMBASE and PubMed were searched in June 2020; sixteen articles were deemed relevant comprising eight animal and eight human studies (301 patients). In animals, BCG administration led to a 1.9 to 5.5-fold increase in survival rate following HSV challenge (vaginal, corneal, or intraperitoneal inoculations). This beneficial effect was influenced by the dose of BCG (higher better), mode of administration (intradermal better than intraperitoneal), and the interval between vaccination and viral challenge (minimum of 6 days required). In non-randomised human studies that failed to control for a placebo effect, BCG vaccination appeared beneficial in 78% of adults with recurrent herpes genitalis or labialis, with 37% being recurrence-free for an extended period, 41% experiencing less frequent or severe episodes, and only 22% reporting no change. This clinical benefit is consistent with the findings of immunological sub-studies. In the two studies restricted to recurrent herpes labialis, 94% appeared to benefit from BCG. The one randomised controlled trial used an intervention in the control group that has immunomodulatory effects thus limiting interpretation. In conclusion, BCG vaccine is a potential, safe, affordable and readily available candidate to decrease the high burden of disease associated with HSV infection and recurrences, but properly controlled randomised trials are required.

ABBREVIATIONS

- BCG: bacillus Calmette-Guérin
- HSV: herpes simplex virus
- IQR: interquartile range
- RHG: recurrent herpes genitalis
- RHL: recurrent herpes labialis

INTRODUCTION

The herpes simplex virus (HSV), typically associated with orofacial ('cold sore') and genital lesions, is among the most serious human pathogens.[1] HSV encephalitis for example, is a severe infection of the central nervous system with a poor prognosis even with antiviral treatment.[2] After primary infection, the virus establishes life-long latency in sensory neurons, and reactivates at variable frequency manifesting as lesions around the initial point of entry - commonly the oral or genital mucosa.[1] Recurrent HSV infections are unpredictable and can be painful and disabling, seriously impacting quality of life. Recurrent ocular infections can significantly affect vision and are a common cause of corneal blindness and a reason for requiring corneal transplantation.[3] Asymptomatic reactivation may also occur, with significant shedding of virus, with the risk of transmission to vulnerable unprotected hosts, such as neonates or immunocompromised individuals.[4,5] Perinatal exposure to HSV through an infected birth canal, or postnatal exposure following contact with individuals orally shedding HSV, can cause neonatal infections, which can be devastating with high mortality and severe neurological sequelae among survivors despite antiviral therapy.[6]

HSV-1 and HSV-2 are highly prevalent and endemic throughout the world.[7,8] In most populations between 65% and 95% of individuals acquire HSV-1,[7] and between 14% and 40% have frequent recurrent herpes labialis (RHL).[9-11] Approximately one fifth of the global population acquires HSV-2,[8] and it is estimated that between 20% and 50% have recurrent herpes genitalis (RHG),[12] resulting

in more than 300,000 years lived with disability in 2013 according to the Global Burden of Disease Study.[13] However, this estimate does not include disability due to neonatal herpes, nor the contribution of genital HSV to HIV susceptibility, which are both underestimated consequences of RHG.[13,14]

Antiviral agents are only moderately effective for treating HSV infection and recurrences, highlighting the need for developing novel prevention measures. Despite ongoing research, there is still no preventive or therapeutic vaccine available against HSV,[14] and no intervention has been successful in stopping HSV recurrences.[12,15] Oral long-term suppressive therapy with acyclovir, valacyclovir, or famciclovir is somewhat effective in reducing the frequency, severity and duration of episodes in adults with RHL or RHG, and in preventing transmission to seronegative individuals, but none fully prevent HSV recurrences and spreading.[12,15,16]

The Bacillus Calmette-Guérin (BCG) vaccine has a beneficial impact beyond its intended scope.[17] Examples include the treatment of non-invasive bladder cancer, melanomas, lung and prostate cancer,[18-23] and protection against progression of autoimmune diseases including diabetes and multiple sclerosis.[24] In randomised controlled trials (RCTs) in high-mortality settings, BCG vaccination has also been associated with protection against unrelated infectious diseases, with up to 50% reduction in all-cause infant mortality.[25] There is also evidence suggesting that BCG vaccination induces off-target (‘non-specific’) protection against a variety of viral infections,

including HSV.[26] The aim of this review was to evaluate the quality of the evidence reported by studies investigating the impact of BCG vaccination on HSV recurrences.

METHODS

Medline and EMBASE were searched in June 2020 with no language restriction. PubMed was also searched to retrieve items not indexed in Medline. The search strategy is detailed in the supplementary material. All studies investigating the effectiveness of BCG vaccination to protect against HSV were included, with no language restriction (Figure 1). For the studies that reported the proportion of participants benefitting from the intervention, data were included in a summary diagram (Figure 2). Of 193 unique articles, sixteen were deemed relevant and are summarised in Table 1 (eight animal studies) and Table 2 (eight human studies). The references of all relevant publications were reviewed and no further articles were identified.

RESULTS

Animal studies

A total of eight studies evaluated the impact of BCG administration (intradermal, intraperitoneal, or intravenous) 2 days to 4 weeks before an HSV challenge (vaginal, corneal, or intraperitoneal instillations) in mice, rabbits or guinea pigs, compared to non-vaccinated controls. In four studies, antiserum was also administered in some of the conditions, 4 hours before or 24 hours after the HSV challenge. One study tested the adoptive transfer of leucocytes from BCG-vaccinated animals

to BCG-naïve animals. Most studies compared survival rates between groups, one study compared the clinical severity of the primary infection, and one study reported prevention of recurrence. These studies are summarised in Table 1.

BCG for prevention of death

In the largest study, the overall survival rate was 2.3-fold higher after various viral challenges in 402 mice receiving intravenous BCG (41.3%) compared to 434 control mice (17.7%). In particular, these rate were 5.5-fold higher following HSV-1 intraperitoneal challenge, and 1.9-fold higher following HSV-2 intraperitoneal challenge. Survival rate were increased in vaccinated mice pre-treated with antiserum 4 hours prior to the viral challenge.[27] In another study, intravenous BCG was associated with a 4.3-fold increased survival rate in rabbits following HSV-2 corneal scarification challenge 4 weeks after vaccination compared to non-vaccinated controls (73% vs. 17%).[28] A third study reported a 4.1-fold higher overall survival rate associated with intraperitoneal BCG following HSV-2 intraperitoneal challenge 10 to 14 days after vaccination, with better rate in mice receiving higher dose of BCG (87-93% survival for doses 100-1000 µg) compared to those receiving lower doses (47% survival for doses 50-63 µg).[29] In another study, involving newborn mice immunised with intraperitoneal or intradermal BCG, survival rates were overall 2-fold higher following HSV-2 intraperitoneal challenge 6 days after vaccination compared with unvaccinated controls, and those receiving the highest dose of intradermal BCG had the best survival rate (3.5-fold higher). Survival rates were 6-fold higher in vaccinated mice given antiserum 24 hours after the HSV-2 challenge

than in controls. These beneficial effect were not observed in mice not vaccinated, or those challenged earlier (2 or 4 days after BCG vaccination). [30] Another study reported on the combination of intravenous BCG with anti-HSV-2 serum and showed a decreased mortality rate following intravaginal challenge with HSV-2 (20%, vs 70% in controls), which was lower than in groups receiving either intervention alone (BCG only: 77% mortality; antiserum only: 50% mortality).[31] Finally, according to a conference abstract, BCG prevented death from encephalomyelitis in all rabbits challenged with intradermal HSV-2 (mortality rate 0%, vs 100% in controls). A similar degree of protection was observed in control rabbits who received leucocytes from BCG-immunised rabbits and anti-HSV-2 serum.[32]

BCG for prevention of recurrence or severity of primary infection

The two last studies reported on BCG vaccination given to decrease the severity of primary infection or prevent recurrences. In the first study, intraperitoneal BCG had no influence on the severity of herpetic keratitis following HSV-1 intracorneal challenge in rabbits and guinea pigs.[33] In the second, intradermal BCG was associated with a slightly lower recurrence rate of herpetic keratitis 2 months after HSV ocular challenge in rabbits, compared with controls immunised with a saline solution.[34]

Human studies

A total of eight studies reported on the impact of BCG vaccination on HSV recurrences in humans: one RCT,[35] six prospective trials,[36-41] and one retrospective study,[42] involving a total of 301 individuals, including 127 with RHL, 162 with RHG, and 12 after their first episode of herpes genitalis (Table 2). Three of the studies were restricted to adults with RHG,[35-37] two were restricted to RHL,[38,39] and the remaining three included both RHL and RHG participants.[40-42] Only one study included children.[41] The BCG vaccine was given intradermally in all studies but the dose and strain varied between studies. Investigators reported on the frequency, severity and duration of recurrences after vaccination, or on the duration of recurrence-free period. The duration of the total follow-up period was rarely specified, and virological confirmation of recurrences was done in one study only.

BCG for prevention of recurrent herpes genitalis

In the RCT, 155 adults with active herpes genitalis (first episode or recurrence) were randomised to BCG vaccination or to an intradermal injection of *Candida* sp. antigen and were followed for approximately 10 months. The mean frequency of recurrence was unchanged after BCG vaccination, but was lower among those with RHG receiving intradermal *Candida*. The authors did not report on the proportion of participants with no further recurrences.[35]

In a prospective study of 38 adults with “severe and therapeutically recalcitrant” RHG (at least 4 episodes per year for an average duration of 2.6 years), BCG vaccination was given once a month

for a maximum of 6 total doses. The intervention was beneficial for the majority of the participants (63%), with 8 (21%) remaining recurrence-free and 16 (42%) experiencing fewer or milder episodes, while 13 participant (34%) did not report any change in frequency or severity of recurrences, and 1 participant (3%) reported worsened symptoms (Figure 2).[36]

In another prospective study, BCG was administered to 30 adults with RHG, inducing a "higher rate of clinical control and milder recurrence" when compared to 15 non-vaccinated adults with RHG. Unfortunately the authors do not provide any further details.[37] However, they evaluated the participants' immune function and detected a Th1/Th2 imbalance in all 45 patients with RHG, with fewer IFN-γ-producing subsets and a low level of IL-12-producing $CD8^+$ T-cells, which normalised after BCG vaccination, reaching similar levels to healthy controls.

BCG for prevention of recurrent herpes labialis

In two studies, nearly all participants benefitted from BCG vaccination: 15 (48%) remained symptom-free, 14 (45%) "improved clearly", and only two participants "did not respond" (6%). Clinical improvement was associated with significant changes in an in-vitro test (HSV-Ag-induced leukocyte migration inhibition test), which remained unchanged in the two non-responders.[38,39]

BCG for prevention of recurrent herpes genitalis or labialis

The last three studies included a mix of participants with either RHG or RHL. In a trial in 12 adults with RHG and three adults with RHL, the median number of recurrence per year decreased from 10 episodes (IQR 5.8-12.0) to none (IQR 0-1.5) after receiving 1 to 2 doses of BCG, and the duration of recurrence-free period between relapses increased from a median of 1.2 months (IQR 1.0-2.1) to a median of 13 months (IQR 6.5-19.0) after vaccination.[40] The majority of the participants (53%) did not report any further recurrences after BCG vaccination, four participants (27%) reported having fewer episodes, and 3 participants (20%) noted no changes. Among the 7 participants with recurrences, three had remained recurrence-free until they had a recurrence during pregnancy. Among the 5 remaining non-pregnant participants, the recurrence was with another HSV type for three (therefore potentially a non-primary first episode), and in two it was with the same virus type (true recurrence). Tuberculin skin testing were done regularly and a negative reaction (after BCG vaccination or transitorily during pregnancy) was associated with recurrence, and a positive reaction after re-vaccination was associated with an absence of recurrence.[40]

In a trial in 109 participants with mainly RHL (98 RHL, 11 RHG), the frequency and duration of recurrences were significantly reduced after BCG vaccination.[41] All participants remained recurrence-free for at least 4 to 6 months, 21 (19%) for 3 years, and 10 (9%) for more than 6 years. This is the only trial that included children, with participants' age ranging between 7 and 58 years (mean 30.6).[41]

In the third study, a retrospective analysis, 20 adults RHL (n=8) and/or RHG (n=13) received 1 to 9 doses of BCG at 10- to 14-day intervals. They found that 35% of the patients had no recurrences, 45% had fewer and less severe recurrences, and only 20% had no change after BCG vaccination.[42]

DISCUSSION

After a growing interest in the ability of BCG vaccine to protect against HSV in the 1970s, research on this topic diminished despite promising results. In human studies, BCG vaccination was perceived as beneficial in 78% of individuals with RHG or RHL, with 37% being recurrence-free for an extended period, 41% experiencing less frequent or severe episodes, and only 22% reporting no change. In the two studies restricted to RHL, BCG vaccination was associated with higher rates of protection; 48% remaining recurrence-free and 45% clearly improving. In another large trial, including mainly individuals with RHL, all remained episode-free for at least 4 to 6 months, and 9% for more than 6 years.

Albeit promising, these results are from non-randomised observational studies, using various BCG strains and doses, different durations of follow-up, and are based mainly on subjective individual report, as virological confirmation was done in one study only. The findings of the single RCT is non-contributory as the two groups had different baseline characteristics, and that the control group also received an intervention, presumably beneficial. Indeed, *Candida* sp. skin test antigen is also

known to induce non-specific immunomodulation,[43,44] and, as suggested by the results of the trial, could therefore also prevent HSV recurrences.

In all the animal studies, BCG vaccination was associated with improved survival following viral challenge; this effect was influenced by the dose of BCG, the mode of administration and the timing between vaccination and viral challenge: higher BCG doses resulted in higher survival rate, intradermal BCG was superior to intraperitoneal BCG, and a minimum of 6 days interval were required between vaccination and the challenge to show benefit.[30] The latter finding is in line with previous findings suggesting that BCG-mediated immunomodulation can be observed as early as 4 to 7 days after vaccination in mice.[45,46] A similar degree of protection were observed in non-vaccinated animals transfused with leucocytes from BCG-vaccinated animals and anti-HSV-2 serum,[32] highlighting the potential role of BCG-induced changes in the blood cells of vaccine recipients. This adoptive transfer experiment, reporting a dramatic beneficial effect on mortality, was reported in a conference abstract only and should therefore be interpreted with caution.

Despite wide heterogeneity in methodology, results from both the human and animal studies suggest that BCG vaccination improves the host's immune response against HSV. This is in line with previous reports of the beneficial non-specific effect of BCG vaccination,[17-25] and in particular against viral pathogens.[26] The underlying immunological and molecular mechanisms underlying these effects are not yet fully understood but are believed to be due to the ability of BCG to induce (i) non-specific memory in innate immune cells ('trained immunity') mediated by epigenetic and

metabolic rewiring, and (ii) heterologous lymphocyte responses, resulting in enhanced immune responses to secondary unrelated infectious agents.[20,26,47,48]

Given the high burden of disease associated with HSV infection, in particular in neonates, encephalitis, and recurrent corneal, labial and genital infections, and in absence of a definite cure, preventive interventions are needed. The results of this review suggests that BCG vaccine is a potential candidate, particularly in light of its availability, affordability and known safety profile. However, the evidence to date is predominantly from non-randomised studies. Before BCG can be recommended for prevention of RHG or RHL, further properly controlled RCTs are required to provide further information, including the influence of BCG strain, optimal dosing and need for repeat dosing, and for which patients and which type of HSV recurrences this intervention is most beneficial.

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Table 1: BCG vaccination for protection against herpes simplex challenge in animal studies

Citation	Study group	Outcome	Key Result
Prevention of death following viral challenge			
Floc'h *et al.* 1976 [27]	P: 4-6wo CD-1 or OF-1 mice I: BCG i.v. (Pasteur, 1mg≅10^6 B) +/- antiserum 4h prior chal. Chal.: 15-31d later, HSV-1 or HSV-2 i.p., or other virus, various routes	Death following challenge (BCG vs. no BCG)	Overall: 58.7% (236/402) vs 82.3% (357/434), p<.001 **-HSV-1 i.p. challenge: 40% (18/45) vs 89% (40/45), p<.001** **-HSV-2 i.p. challenge: 55% (39/71) vs 76% (54/71), p=.008**
Larson *et al.* 1972 [28]	P: Angora, New Zealand, and Dutch-belted rabbits I: BCG i.v. (4*10^7 B) Chal.: 4w later, HSV-2 vag. or i.c.	Death following challenge (BCG vs. no BCG)	**i.c. scarification: 27% (8/30) vs 83% (25/30), p<.001** I.c. injection: 67% (4/6) vs 100% (6/6), p=0.5 Vag. instillation: 62% (8/13) vs 82% (9/11), p=0.3
Glasgow *et al.* 1977 [29]	P: Female white Swiss Webster mice I: BCG i.p. (Paris strain, 200 µg) Chal.: 10-14d later, HSV-2 i.p.	Death following challenge (BCG vs. no BCG)	**47% (7/15) vs 87% (26/30), p<.01** (7-13% for BCG doses 100-1000µg, 53% for BCG dose 50-63 µg)
Starr *et al.* 1976 [30]	P: 1-2do Swiss mice I: BCG i.p. or i.d., full or 1/5 dose (Tice strain, 8*10^8 B/ml) +/- antiserum i.p. 24h after chal. Chal.: 2d, 4d, or 6d later, HSV-2 i.p.	Death after viral challenge (BCG vs. no BCG)	Challenge D2, BCG i.p. (full dose): 90% (28/31) vs 100% (9/9), p=1 Challenge D4, BCG i.p. (full dose): 92% (22/24) vs 100% (9/9), p=1 **Challenge D6, BCG i.p. (overall): 46% (12/26) vs 100% (9/9), p=.005** -Full BCG: 50% (3/6) vs 100% (9/9), p=.04 -1/5 BCG: 45% (9/20) vs 100% (9/9) , p=.005 **Challenge D6, BCG i.d. (overall): 58% (7/12) vs 100% (9/9) , p=.045** -Full BCG: 29% (2/7) vs 100% (9/9) , p=.005 -1/5 BCG: 100% (5/5) vs 100% (9/9)
Baker *et al.* 1974 [31]	P: Female white Swiss mice I: BCG i.v. (1*10^7 B) +/- antiserum 4h prior chal. Chal.: 7-10d later, HSV-2 vag.	Death after viral challenge	**BCG + antiserum: ~20%** BCG alone: ~77% Antiserum alone: ~50% Control: ~70%
Lehel *et al.* 1978 [32]	P: rabbits I: BCG or adoptive transfer of leucocytes from BCG-immunised rabbit and antiserum (no detail provided, conference abstract) Chal.: HSV-2 i.d.	Death after viral challenge	BCG: 0% Control: 100% Control with leucocyte from BCG-immunised rabbit and antiserum: 0%
Prevention of severity or recurrence			
Smolin *et al.* 1975 [33]	P: guinea pigs and rabbits I: BCG i.p. (Pasteur, 0.5 ml≅$10^{3.5}$ B), 2 doses Chal.: 5d after 2nd BCG dose, HSV-1 i.c. 0.01ml (LD50 10^5/0.03ml)	Herpetic keratitis severity (BCG vs no BCG, mean score)	Guinea pigs: D1: 2.7 (range 2-4) vs 3.3 (range 2-4) D2: 0.9 (range 0-2) vs 1.5 (range 0-4) D3: 0.9 (range 0-2) vs 0.9 (range 0-4) Rabbits: D2: 1.3 (range 1-2) vs 1.4 (range 1-2) D3: 1.9 (range 1-3) vs 2.1 (range 1-3)

			D4: 2.2 (range 1-3) vs 2.1 (range 1-3) D7: 2.7 (range 1-4) vs 2.6 (range 1-4) D9: 1.7 (range 0-3) vs 1.5 (range 0-3)
Kaufman *et al.* 1975 [34]	P: New Zealand rabbits I: BCG i.d. (Pasteur, 4x0.6-0.7ml≅4.5-5.3mg, into each hind-foot pad and behind each ears) Chal.: 15d later, HSV i.c. (McKrae)	Herpetic lesion (BCG vs no BCG, mean number of lesion/cornea/ rabbit)	D52-58: 4.41 (SD 5.07) vs 4.03 (SD 4.75) **D59-65: 2.85 (SD 4.74) vs 7.00 (SD 8.90), p<.05** D66-72: 6.69 (SD 9.05) vs 7.54 (SD 11.56) D73-79: 5.54 (SD 7.57) vs 4.25 (SD 5.63) D80-84: 3.04 (SD 4.23) vs 4.77 (SD 8.11)

BCG: Bacille Calmette-Guérin; chal.: challenge; d: day; i.c.: corneal; i.d.: intradermal; i.v.: intravenous; mo: months-old; vag.: intravaginal; wo: weeks-old.

Table 2: BCG vaccination for reducing the recurrence and severity of herpes labialis and genitalis

Citation Country	Study group	Study type	Outcome	Key results
Prevention of recurrent herpes genitalis				
Douglas *et al.* 1985 [35] USA	155 adults (mean age 27.2y, SD 6.8) with RHG (n=134) *or* FHG (n=21) Gp1: BCG Glaxo strain (0.1ml≅2*10^5 B), n=83 (71 RHL, 12 FHG) Gp2: *Candida* sp. skin test antigen 0.1ml i.d., n=72 (63 RHL, 9 FHG)	Double-blind RCT	Frequency of recurrence	Before BCG: 0.608/m, SD 0.412 After BCG: 0.528/m -among RHG: 0.532/m Before *Candida*: 0.747/m, SD 0.502 After *Candida*: 0.392/m (*p*=.08, vs BCG) -among RHG: 0.357/m (*p*<.002, vs BCG)
Bierman 1976 [36] USA	38 adults (mean age 33y, range 20-57) with RHG BCG Glaxo strain 1ml 1x/m, max 6 doses	Interventional study	Frequency and severity of recurrence	8 (21%) no recurrences 16 (42%) fewer and milder episodes 13 (34%) no change in frequency or severity 1 (3%) worsened
			Side effect	9 (24%), abscess at site of inoculation
Deng *et al.* 2004 [37] China	45 adults with RHG BCG (no detail provided)	Interventional study	Frequency and severity of recurrence	"Higher rate of clinical control and milder recurrence in the BCG group" compared to 15 non-vaccinated adults
Prevention of recurrent herpes labialis				
Jarisch *et al.* 1977 [39] Austria	8 adults with RHL BCG Berna (0.1ml≅8-26*10^5 B)	Interventional study	Frequency and severity of recurrence	5 (63%) had no recurrence 3 (38%) had shorter episodes
Jarisch *et al.* 1979 [38] Austria	23 adults (mean age 33y, range 18-52) with RHL BCG Berna (0.1ml≅8-26*10^5 B)	Interventional study	Frequency and severity of recurrence	10 (44%) remained symptom-free 11 (48%) "improved clearly" 2 (9%) "did not respond"
Prevention of recurrent herpes genitalis or labialis				
Anderson *et al.* 1974 [40] USA	15 adults with RHG (12) or RHL (3) BCG Glaxo (0.1ml≅5*10^5 B) Some received a second dose	Interventional study	Frequency and severity of recurrence	8 (53%) had no recurrences 4 (27%) had fewer episodes 3 (20%) noted no change Before BCG: median 10/y, IQR 5.8-12.0 After BCG: median 0/y, IQR 0-1.5
			Time between recurrences	Before BCG: median 1.2 m, IQR 1-2.1 After BCG: median 13 m, IQR 6.5-19

Hippmann *et al.* 1992 [41] Austria	109 individuals (mean age 30.6y, range 7-58) with RHL (98) or RHG (11) BCG Berna (0.1ml≅8-26*10^5 B)	Interventional study	Duration of recurrence-free period	109 (100%) for ≥4-6m 21 (19%) for ≥3y 10 (9%) for ≥6y
Fanta *et al.* 1977 [42] Austria	20 adults (mean age 42y, range 26-65) with RHL (n=8) and/or RHG (n=13) BCG Pasteur 0.05 ml, then 0.1ml every 10-14d (1 to 9 total doses)	Retrospective	Frequency and severity of recurrence	7 (35%) had no recurrences (“only prodromal symptoms”) 4 (20%) rare episodes, less severe, shorter duration 5 (25%) fewer episodes, less severe 4 (20%) noted no change

B: bacilli; BCG: Bacille Calmette-Guérin; FHG: first episode of herpes genitalis; Gp: group; HSV: herpes simplex virus; IQR: interquartile range; m: month; n: number of participant; RCT: randomised control trial; RHG: recurrent herpes genitalis; RHL: recurrent herpes labialis; SD: standard deviation; USA: United States of America; y: year.

FIGURES LEGEND

Figure 1: PRISMA flow diagram of systematic review

Figure 2: Clinical response to BCG vaccination in adults with recurrent HSV infections

BCG: Bacille Calmette-Guérin; HSV: herpes simplex virus; RHG: recurrent herpes genitalis; RHL: recurrent herpes labialis.
In the study by Fanta *et al*, one patient reported both RHG and RHL.[42]