Herpes Simplex Virus (HSV) Type 2 Glycoprotein D Subunit Vaccines and Protection against Genital HSV-1 or HSV-2 Disease in Guinea Pigs

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In two recent clinical trials, a vaccine containing herpes simplex virus (HSV) type 2 glycoprotein D (gD2) and a novel adjuvant AS04 comprising alum (Al) and 3-deactylated monophosphoryl lipid A (3-dMPL) afforded HSV-seronegative women significant protection against HSV-2 genital disease (vaccine efficacy, 73% in study 1 and 74% in study 2) and limited protection against infection (46% in study 1 and 39% in study 2). In the present report, studies in the guinea pig model investigated the protection afforded by gD2/AS04 against HSV-1 and HSV-2 genital herpes and investigated whether immunization could prevent or reduce recurrent disease in guinea pigs that developed mucosal infection. Immunization with gD2/AS04 conveyed nearly complete protection against primary disease with either virus but did not prevent mucosal infection. Guinea pigs immunized with gD2/AS04 were significantly better protected against recurrent disease than were guinea pigs immunized with a gD2/Al vaccine, which suggests that inclusion of 3-dMPL improved protection against latent infection.

Genital herpes is a common sexually transmitted disease [1, 2]. Although herpes simplex virus (HSV) type 2 is the most common cause of genital herpes in the United States [3], HSV-1 accounts for about one-third of new cases annually and is the most common cause of genital herpes in some countries [4–6]. Initial ano-genital HSV infection can be a painful illness characterized by vesicular and ulcerative skin lesions and neurologic and urologic complications. During the initial infection, a lifelong latent infection of sacral ganglion neurons is established, reactivation of which causes recurrent genital disease that can also be painful [7]. In addition to the pain and discomfort associated with initial and recurrent infections, genital herpes causes substantial psychological morbidity [8, 9], may increase the risk of acquiring human immunodeficiency virus infection [10, 11], and can be spread to susceptible sex partners and to fetuses or newborn infants [12, 13]. Despite the availability of effective antiviral drug therapy [2], the prevalence of genital herpes in the United States continues to increase [3], with the estimated direct costs of genital herpes now >$200 million annually [14]. Given the magnitude of the problem, effective vaccines represent the best strategy for control of genital herpes.
However, despite >60 years of research, the development of an effective HSV vaccine has remained elusive. In the recent past, considerable attention has been focused on subunit vaccines produced by means of recombinant genetic techniques [15]. Two highly immunogenic HSV envelope proteins, glycoproteins B (gB) and D (gD), have been selected for commercial development. A vaccine containing HSV-2 gB and gD with MF59, an oil-in-water emulsion adjuvant system, was developed by Chiron. This vaccine was highly immunogenic in humans but failed to protect volunteers against genital HSV-2 infection in phase 3 trials [16, 17]. A second vaccine has been developed by GlaxoSmithKline Biologicals; this vaccine contains HSV-2 gD (gD2) and a novel adjuvant system, AS04 [18], which contains aluminum hydroxide (Al) and 3-deactylated monophosphoryl lipid A (3-dMPL), a modified form of the lipid A component of the lipopolysaccharide of gram-negative bacteria. In 2 phase 3 trials, the gD2/AS04 vaccine had an efficacy of 73% and 74% against development of symptomatic HSV-2 genital herpes in HSV-seronegative women and limited efficacy (46% and 39%) against HSV-2 infection [19].

In this report, we examined how immunization with the gD2/AS04 vaccine affected the natural history of genital HSV infection in a guinea pig model that closely mimics human disease. Intravaginal inoculation with HSV is followed by viral replication in the genital mucosa and the development of a self-limiting primary vesiculoulcerative genital skin disease [20], which is followed by episodic spontaneous recurrent lesions [21]. Both HSV-1 and HSV-2 can cause genital skin disease, producing similar primary infections, but the incidence and frequency of recurrent disease is higher in HSV-2–infected guinea pigs [22], as it is in humans [23]. Thus, the model allows for the assessment of a number of outcome measures relevant to vaccine efficacy, including the ability to protect against mucosal infection, genital tract disease resulting from the initial infection, and the subsequent development of recurrent HSV infections, which is an indirect measure of latency [24]. The studies described here addressed 2 questions of clinical importance: does the HSV-2 vaccine protect equally against genital HSV-1 and HSV-2 infection and disease and, if the vaccine does not protect against mucosal infection, does it affect the natural history of recurrent disease?

MATERIALS AND METHODS

Animals. Female Hartley guinea pigs (250–350 g) were obtained from Charles River Breeding Laboratories and housed under conditions approved by the American Association for the Accreditation of Laboratory Animal Care.

Vaccines. The experimental vaccines contained a recombinant HSV-2 gD2 combined with adjuvant. The recombinant protein, which lacked the carboxyl-terminal membrane anchor domain, was purified from the cell culture supernatant of CHO cells transfected with the truncated gD2 gene. All vaccines were prepared by GlaxoSmithKline Biologicals. The formulations were as follows: vaccine 1 (gD2/Al), gD2 (5 μg) with aluminum hydroxide (500 μg); vaccine 2 (gD2/AS04), gD2 (5 μg) with aluminum hydroxide (500 μg) and 3-dMPL (50 μg); and AS04 adjuvant control (ADJ), aluminum hydroxide (500 μg) and 3-dMPL (50 μg).

Experimental design. One hundred eight guinea pigs were randomly assigned to 8 groups: groups 1 and 5 (n = 12 each) were unimmunized control guinea pigs, groups 2 and 6 (n = 12 each) were control guinea pigs that received ADJ, groups 3 and 7 (n = 15 each) received gD2/Al, and groups 4 and 8 (n = 15 each) received gD2/AS04. Guinea pigs were immunized on days 99, 64, and 15 before virus inoculation. Each 0.5-mL dose of vaccine or ADJ was administered by subcutaneous injection at 5 separate sites on the dorsum.

One day before viral challenge, blood samples were obtained from guinea pigs by toenail clip, and the serum was stored at −20°C. Guinea pigs were inoculated with virus by rupture of the vaginal closure membrane with a moistened calcium alginate tipped swab (Calgiswab #3; Spectrum Laboratories) and instillation of 0.1 mL of a virus suspension containing 5.7 log_{10} pfu of HSV-1 strain 17 syn + (groups 1–4) or HSV-2 strain MS (groups 5–8) into the vaginal vault by means of a plastic catheter (Abbocath; Abbott Laboratories). Swab samples of cervicovaginal secretions were collected on days 1, 2, 3, 5, 7, and 10 after inoculation and were stored frozen (−70°C) until being assayed for virus on primary rabbit kidney cells [25]. Guinea pigs were evaluated daily, and primary genital skin disease was quantified by use of a lesion score scale, ranging from 0 (no disease) to 4 (severe vesiculoulcerative skin disease of the perineum). The area under the lesion score–day curve was used as a measure of disease severity [20]. After recovery from primary infection, guinea pigs were examined daily during days 22–63 after inoculation for evidence of spontaneous recurrent herpetic lesions [21]. The number of lesion-days (days on which a recurrent lesion was observed on the perineum) was used as a measure of the frequency of recurrent disease.

ELISA for gD2-specific IgG. ELISAs were carried out in 96-well microtiter plates (Maxisorp Immuno-plate). Antigen was applied to the plates by allowing 50 μL/well of a 1-μg/mL solution of gD2 in PBS to adsorb overnight at 4°C. Plates were then washed 5 times with wash buffer (PBS containing 1% [vol/vol] Tween) and incubated with saturation buffer (wash buffer containing 1% [wt/vol] bovine serum albumin) for 1 h at 37°C. Three-fold dilutions of serum samples (starting at 1:1000 dilution) were prepared in saturation buffer and applied to the antigen-coated plates. After 2 h of incubation at ambient temperature, plates were washed 5 times with wash buffer, and...
IgG-specific biotin-conjugated sheep anti–guinea pig IgG (50 μL/well; Serotec; Sopar Biochemicals) diluted in saturation buffer was added. Plates were incubated for 90 min at 37°C, washed 5 times with wash buffer, and incubated for 30 min at 37°C with streptavidin-peroxidase complex (Amersham) diluted 1:1000 in saturation buffer. After being washed 5 times with wash buffer, plates were incubated with 0.1 M citrate buffer (pH 4.5) containing 0.04% (wt/vol) o-phenylenediamine (Sigma) and 0.03% (vol/vol) hydrogen peroxide. Midpoint ELISA titers were calculated by computerized 4-parameter nonlinear regression analysis and were defined as the reciprocal of the serum dilution that produced an absorbance (at 492 nm) equal to 50% of the maximum value.

Neutralization assays. Serial 2-fold dilutions of serum samples (50 μL/well) were prepared in duplicate in 96-well microtiter plates (Nunc). Fifty microliters of a mixture containing 3.6 log₁₀ pfu of HSV-2 strain HG52 and complement (1:100 of the final dilution) was added to each well. Plates were incubated for 1 h at 37°C, 0.1 mL of a suspension containing 4.6 log₁₀ baby hamster kidney cells was added to each well, and the plates were incubated for a further 3 days at 37°C in the presence of 7% CO₂. After removal of the culture medium, the plates were stained with crystal violet, washed, and examined for viral plaques. The neutralizing titer was defined as the reciprocal of the highest serum dilution at which no viral plaques were detected (100% protection from cytopathic effect). By use of this assay, complete cytopathic effect (100% lysis of the cell monolayer) was seen in control wells.

Statistics. For comparisons between 2 groups, data were analyzed by Student’s t test or Fisher’s exact test, as appropriate. Comparisons of multiple groups were made by 1-way analysis of variance with Bonferroni correction. All comparisons are 2-tailed.

RESULTS

Vaccine immunogenicity. Figure 1 shows the gD2-specific ELISA and HSV-2–neutralizing antibody titers present in the serum of immunized guinea pigs 1 day before virus challenge. All guinea pigs that were administered vaccine formulations containing gD2 developed HSV-specific humoral immune responses following immunization. Unimmunized and ADJ-immunized control guinea pigs did not develop detectable humoral immune responses.

Genital tract infection. Guinea pigs were defined as infected if virus was isolated by plaque titration assay from cervicovaginal secretions collected 24–48 h after intravaginal HSV challenge. By this definition, 21 (91%) of 23 HSV-1– and 22 (92%) of 24 HSV-2–infected control guinea pigs (i.e., unimmunized and ADJ-immunized groups) became infected. The virus titers in vaginal secretions of HSV-1– or HSV-2–challenged ADJ-immunized control guinea pigs were similar to those of the unimmunized control guinea pigs on both day 1 and day 2 after virus inoculation (table 1). In addition, the duration of HSV-1 or HSV-2 replication in the genital tract was similar for both control groups (figure 2). Thus, immunization with adjuvant alone did not affect the magnitude or duration of viral replication in the genital mucosa.

Among guinea pigs challenged with HSV-1, immunization with gD2-containing subunit vaccines protected a small proportion against mucosal infection; 12 (40%) of 30 immunized guinea pigs were uninfected, compared with 2 (9%) of 23 control guinea pigs (P < .05). When the 2 vaccine formulations were analyzed separately, only the gD2/Al vaccine provided significant protection, compared with the combined control guinea pigs (P < .05; table 1). Although immunization only marginally affected the HSV-1 infection rate, both vaccine formulations significantly reduced virus titers in the genital tracts of infected guinea pigs on days 1 and 2 after inoculation (P < .01 for each; table 1), resulting in a shortened duration of viral shedding (figure 2).

In guinea pigs challenged with HSV-2, gD2-containing vaccines afforded no protection against mucosal infection; 6 (20%)
of 30 immunized guinea pigs were uninfected, compared with 2 (8%) of 24 control guinea pigs (P > .05). Furthermore, when analyzed separately, neither formulation protected against mucosal infection. However, guinea pigs immunized with gD2/Al had significantly lower virus titers in cervicovaginal swab samples on day 1 after inoculation (P < .01), whereas those immunized with gD2/AS04 had significantly lower titers on both days 1 and 2 after inoculation (P < .001, day 1; P < .01, day 2). As with HSV-1–challenged guinea pigs, immunization with either vaccine resulted in a reduction in the duration of HSV-2 shedding in the genital tract (figure 2).

**Disease resulting from primary infection.** Table 2 summarizes the effect of immunization on the incidence and severity of primary genital herpes. Although immunization afforded little or no protection against mucosal infection, it did provide significant protection against disease resulting from the infection. Twenty (95%) of the 21 unimmunized and ADJ-immunized control guinea pigs infected with HSV-1 developed characteristic herpetic skin lesions during primary infection (table 2). The 2 control groups were comparable with regard to the incidence of hindlimb paralysis, mortality, and the incidence and severity of primary genital skin disease. Immunization with either gD2 formulation provided complete protection from the cutaneous and neurologic manifestations of disease resulting from HSV-1 genital tract infection.

With regard to disease resulting from HSV-2 challenge, 21 (95%) of 22 control guinea pigs developed genital skin disease during the primary infection (table 2). There was no difference between the 2 control groups in the incidence of disease, hindlimb paralysis, or death. However, ADJ-immunized guinea pigs did experience less-severe skin disease than did unimmunized control guinea pigs (P < .005). Immunization with either gD2 formulation significantly reduced the incidence of primary skin disease resulting from HSV-2 genital tract infection, compared with either control group (P < .001), with only a single guinea pig in each of the 2 vaccine groups developing evidence of mild herpetic skin disease.

**Recurrent disease.** After recovery from the initial infection, all surviving guinea pigs were evaluated for episodic recurrent disease. The evaluation of recurrent infection was complicated by the severity of primary disease in control groups (particularly in HSV-2–challenged guinea pigs). Many guinea pigs either died or had extensive damage to the perineum, which precluded evaluation for recurrent lesions. Because only guinea pigs that could be accurately assessed from days 22 to 63 after inoculation were included, the number of guinea pigs was small, even after appropriate control guinea pigs were combined. Results are shown in table 3. Recurrent disease developed in 5 (42%) of 12 HSV-1– and all 3 HSV-2–infected control

![Figure 2](https://academic.oup.com/jid/article-abstract/187/4/542/832857)
guinea pigs, with HSV-2–infected guinea pigs experiencing significantly more recurrent disease (P < .01).

Only 1 HSV-1–infected guinea pig from each vaccine immunized group developed recurrent disease, and both of these guinea pigs experienced only a single lesion-day during the 42-day observation period. HSV-2–infected guinea pigs immunized with gD2/Al developed significantly fewer recurrences than did control guinea pigs (P < .02). However, although only 1 (7%) of 14 gD2/Al-immunized guinea pigs exhibited signs of primary genital herpes, recurrences were observed in 9 guinea pigs, which indicates that the subclinical genital tract infection resulted in the establishment of a latent infection that was sufficiently robust to produce recurrent infections. In contrast, only 1 gD2/AS04-immunized guinea pig developed recurrences, the same guinea pig that had previously experienced symptomatic primary infection. Thus, the incidence of recurrent disease was significantly lower in the gD2/AS04 group than in control guinea pigs (P < .05) and in gD2/Al-immunized guinea pigs (P < .01).

DISCUSSION

In recent phase 3 clinical trials of HSV-2–discordant couples, a gD2/AS04 vaccine provided HSV-seronegative women with significant protection against HSV-2 genital herpes disease and limited protection against HSV-2 infection [19]. Among questions that were not addressed in the clinical trials were whether the vaccine could protect against HSV-1 genital herpes and whether vaccine recipients who became infected were afforded some protection against latency and subsequent recurrent infections. We have used a guinea pig model of genital HSV infection to explore these questions and to compare the gD2/AS04 formulation used in the human clinical trials to a formulation that lacked 3-dMPL.

Because gD is highly conserved between HSV-1 and HSV-2 [26, 27], we hypothesized that the gD2 vaccines would engender cross-protective immune responses that would afford protection against HSV-1 challenge. The present study confirmed this hypothesis, with both gD2 vaccines providing female guinea pigs with complete protection against primary disease resulting from intravaginal HSV-1 challenge. These results suggest that the gD2/AS04 vaccine that protected women against HSV-2 genital disease will also provide protection against HSV-1 genital herpes, a finding with clinical relevance given epidemiologic data indicating the increasing importance of HSV-1 as a cause of genital herpes [1, 4–6].

Both vaccine formulations also provided excellent protection against primary disease after HSV-2 challenge, with only 1 guinea pig in each vaccine group developing mild symptoms. However, in contrast to their efficacy against primary disease caused by either virus, the vaccines provided only modest protection against HSV-2 infection, reducing but not preventing viral replication in the vaginal mucosa of the majority of guinea pigs. This finding is similar to that seen with the gD2/AS04 vaccine in recent clinical trials, in which protection against HSV-2 infection occurred in 39%–46% of HSV-seronegative females [19]. Furthermore, studies with a variety of other experimental HSV vaccines in the guinea pig model and experiments in which guinea pigs latently infected with HSV-2 received a second vaginal virus challenge also have failed to prevent viral replication in the genital tract, suggesting that it may be very difficult to provide immunologic protection of mucous membranes against challenge with high virus inocula [24, 28–32].

It is uncertain whether a vaccine that prevented primary herpes disease but not infection would affect the spread of genital herpes. The likelihood that this would occur was increased if vaccine recipients who became infected had fewer recurrent infections than did unimmunized persons with genital herpes. By use of a nucleic acid vaccine in the guinea pig model, we have shown elsewhere [24] that prophylactic immunization can reduce the magnitude of latent viral infection and that this reduction correlates with a decrease in recurrent infections. Consequently, a second aim of these studies was to determine whether these vaccines modify recurrent disease. We found that guinea pigs immunized with the gD2/Al vaccine experienced significantly fewer recurrences than did HSV-2–infected control guinea pigs; however, recurrences were observed in 9 of 15 guinea pigs, including 8 that had experienced only subclinical primary infection. Substantially greater protection was seen with the gD2/AS04 vaccine, in which only 1 guinea pig developed recurrent HSV-2 infections was the guinea pig that had disease associated with primary infection. None of the gD2/AS04-immunized guinea pigs that experienced subclinical primary infection developed recurrent disease. These results suggest that inclusion of 3-dMPL engendered immune responses that provided greater protection against latent infection and subsequent recurrent HSV-2 disease than was observed with alum alone. The use of MPL as an adjuvant has been reported to stimulate Th1-type responses to immunization in vaccinated guinea pigs and humans [33, 34] (authors’ unpublished data). Th1-type, rather than Th2-type, immune responses may be needed to control HSV infections and, in particular, to protect the sensory ganglia from acute infection [35–38].

Regarding the impact of immunization on HSV-1 recurrences, both vaccine formulations afforded excellent protection against recurrent disease in HSV-1–infected guinea pigs, with only 1 guinea pig from each immunized group experiencing a single recurrent episode. This apparent protection against recurrent HSV-1 genital herpes might have been facilitated by the natural history of HSV-1 genital infection, which typically
results in a lower incidence and frequency of recurrent infections than does HSV-2 [22, 23].

As with all animal models of human disease, it is important to remember that the guinea pig model of genital herpes is indeed a model. The immune responses to immunization and the mechanism of protection may differ from those in humans, and so care must be taken in interpreting results. With these caveats, the results of these and other studies have implications for establishing expectations for HSV vaccines. They predict that HSV vaccines may not be capable of inducing a sterilizing immunity that will completely protect the genital mucosa from infection [24, 28–32]. However, it is realistic to expect that effective vaccines could protect the subject from developing symptomatic primary disease. If HSV vaccines cannot prevent infection of the genital mucosa, both symptomatic and asymptptomatically infected subjects might establish latent infection and later experience recurrent genital herpes. Immunized persons who become infected might be expected to have fewer recurrences than do those who did not receive a vaccine. A major factor contributing to the spread of genital herpes is the ability of HSV to be shed from the genital tract in the absence of recognizable signs or symptoms of infection [39, 40]. Thus, it will be important in future vaccine studies to establish their ability to affect asymptomatic shedding as well as recurrent disease. If the frequency or magnitude of this asymptomatic virus shedding is also reduced in immunized subjects, it will increase the likelihood that immunization would reduce the spread of genital herpes.

If immunization does not affect the spread of infection, the major benefits of the vaccine would be to protect the immunized host from experiencing severe initial genital herpes and frequent recurrent infections. Although less than ideal, a vaccine that protected against severe primary and frequent recurrent genital herpes would reduce the substantial physiologic and psychological morbidity associated with symptomatic genital herpes and health care costs associated with treatment of the disease and would be preferable to no vaccine at all. The possibility that people immunized with such a vaccine could subsequently become subclinically infected and inadvertently spread infection to susceptible partners might be addressed by a policy of universal immunization so that, even if exposed, the partner might become infected but would not experience clinical disease. Because HSV vaccines may provide only partial protection against genital infection, it will also be impor-

<table>
<thead>
<tr>
<th>Group</th>
<th>Vaccine</th>
<th>Challenge</th>
<th>Incidence</th>
<th>Severity, mean ± SE</th>
<th>Hindlimb paralysis</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>HSV-1</td>
<td>10/10</td>
<td>7.15 ± 1.13</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>ADJ</td>
<td>HSV-1</td>
<td>10/11</td>
<td>7.90 ± 0.83</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>gD2/Al</td>
<td>HSV-1</td>
<td>0/8</td>
<td>0.00 ± 0.00</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>gD2/AS04</td>
<td>HSV-1</td>
<td>0/10⁶</td>
<td>0.00 ± 0.00</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>HSV-2</td>
<td>10/11</td>
<td>15.05 ± 1.03</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>ADJ</td>
<td>HSV-2</td>
<td>11/11</td>
<td>10.86 ± 0.00</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>gD2/Al</td>
<td>HSV-2</td>
<td>1/14⁷</td>
<td>3.00 ± 0.00</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>gD2/AS04</td>
<td>HSV-2</td>
<td>1/10⁹</td>
<td>2.50 ± 0.00</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. ADJ, adjuvant; Al, alum; AS04, alum plus 3-deactylated monophosphoryl lipid A.

- No. of guinea pigs with clinical disease/no. of guinea pigs infected.
- Severity was measured as the area under lesion score–day curve and was calculated only for symptomatic guinea pigs.
- Defined as paralysis of 1 or both hindlimbs for ≥1 day.
- Includes only guinea pigs that died by day 15 after inoculation.
- , vs. group 1.
- , vs. group 5.
- , vs. group 5.

Table 3. Effect of herpes simplex virus (HSV) type 2 glycoprotein D (gD2) vaccines on recurrent disease.

<table>
<thead>
<tr>
<th>Group</th>
<th>Vaccine</th>
<th>Challenge</th>
<th>Incidence</th>
<th>Recurrences, mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 + 2</td>
<td>None or ADJ</td>
<td>HSV-1</td>
<td>5/12</td>
<td>2.00 ± 0.77</td>
</tr>
<tr>
<td>3</td>
<td>gD2/Al</td>
<td>HSV-1</td>
<td>1/8</td>
<td>1.00 ± 0.00</td>
</tr>
<tr>
<td>4</td>
<td>gD2/AS04</td>
<td>HSV-1</td>
<td>1/10</td>
<td>1.00 ± 0.00</td>
</tr>
<tr>
<td>5 + 6</td>
<td>None or ADJ</td>
<td>HSV-2</td>
<td>3/3</td>
<td>10.67 ± 3.52</td>
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<tr>
<td>7</td>
<td>gD2/Al</td>
<td>HSV-2</td>
<td>9/14</td>
<td>3.56 ± 0.76³</td>
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<tr>
<td>8</td>
<td>gD2/AS04</td>
<td>HSV-2</td>
<td>1/10³</td>
<td>4.00 ± 0.00</td>
</tr>
</tbody>
</table>

- No. of guinea pigs with recurrent lesions/no. of infected guinea pigs that could be evaluated.
- Defined as recurrent lesion–days between days 22 and 63 after inoculation, calculated only for guinea pigs that experienced recurrences.
- , vs. combined control groups.

Table 2. Effect of herpes simplex virus (HSV) type 2 glycoprotein D (gD2) vaccines on vaginal HSV replication.
tant to examine whether immunization reduces the risk of vertical transmission for women who become infected during pregnancy.

In summary, studies using a guinea pig model of genital herpes showed that a subunit gD2 vaccine that, in clinical trials, provided women significant protection against HSV-2 genital disease but limited protection against infection also provided significant protection against genital HSV-2 disease in female guinea pigs. The experiments further showed that gD2 vaccines provided cross-protection against disease resulting from genital HSV-1 challenge. The inclusion of 3-dMPL significantly increased protection against recurrences of genital herpes in infected guinea pigs. These results suggest that the gD2/AS04 vaccine may protect women against both HSV-1 and HSV-2 genital herpes and that women who experience breakthrough infection may experience fewer recurrent infections and, therefore, may be less likely to spread infection to susceptible sex partners or to their fetuses or newborns. Recent mathematical modeling data suggest that widespread use of the vaccine by seronegative women could reduce the spread of genital herpes among both men and women [41]. Collectively, these results support the further development of the gD2/AS04 vaccine.

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References


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