Protection from Herpes Simplex Virus (HSV)–2 Infection with Replication-Defective HSV-2 or Glycoprotein D2 Vaccines in HSV-1–Seropositive and HSV-1–Seronegative Guinea Pigs

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**Background.** A herpes simplex virus (HSV)–2 candidate vaccine consisting of glycoprotein D (gD2) in alum and monophosphoryl lipid A (MPL) reduced genital herpes disease in HSV-1–seropositive women but not in men or HSV-1–seropositive women.

**Methods.** To determine the effect of HSV-1 serostatus on effectiveness of different vaccines, we tested gD2 in alum/MPL, gD2 in Freund’s adjuvant, and dl5–29 (a replication-defective HSV-2 mutant) in HSV-1–seropositive or HSV-1–seronegative guinea pigs.

**Results.** In HSV-1–seronegative animals, dl5–29 induced the highest titers of neutralizing antibody, and after vaginal challenge with wild-type virus, dl5–29 resulted in lower rates of vaginal shedding, lower levels of HSV DNA in ganglia, and a trend for less acute and recurrent genital herpes, compared with the gD2 vaccine. In HSV-1–seropositive animals, all 3 vaccines induced similar titers of neutralizing antibodies and showed similar levels of protection against acute and recurrent genital herpes after vaginal challenge with wild-type virus, but dl5–29 reduced vaginal shedding after challenge more than did the gD2 vaccines.

**Conclusions.** dl5–29 is an effective vaccine in both HSV-1–seropositive and HSV-1–seronegative guinea pigs and was superior to gD2 vaccines in reducing virus shedding after challenge in both groups of animals. dl5–29 Might reduce transmission of HSV-2.

Primary infection with herpes simplex virus (HSV) results in life-long latent infection. HSV-2 is usually latent in sacral ganglia, where reactivation results in genital herpes. HSV-2 can cause neonatal herpes, and HSV-2 infection is a risk factor for acquisition of human immunodeficiency virus [1, 2].

Two trials found that HSV-2 glycoprotein D (gD2) and glycoprotein B (gB2) in MF59 adjuvant failed to protect persons from new HSV-2 infections [3]. Stanberry et al [4] performed 2 trials using gD2 in alum and monophosphoryl lipid A (MPL) and showed that the vaccine reduced genital herpes disease in HSV-1–seronegative women but not in HSV-1–seropositive women or in men. The difference in results in these clinical trials may have been due to differences in adjuvants or immunogens. The HSV-1 serostatus prior to vaccination may also affect the efficacy of an HSV-2 glycoprotein vaccine. Seropositivity for HSV-1 does not significantly reduce the rate of HSV-2 infection [5] but does reduce symptomatic HSV-2 infection [6]. Because seroprevalence rates for HSV-1 are >50% for healthy adults in the United States, the lack of effectiveness of
an HSV-2 vaccine in HSV-1–seropositive women represents a substantial impediment.

Previously we reported that a replication-defective HSV-2 candidate vaccine, HSV-2 dl5–29, and gD2 in complete Freund’s adjuvant followed by incomplete Freund’s adjuvant (CFA/IFA) had similar efficacy for protection against acute and recurrent disease in guinea pigs [7]. HSV-2 dl5–29, however, induced higher levels of neutralizing antibodies in guinea pigs. Few studies have compared the effects of different vaccines and different adjuvants on the effectiveness of HSV-2 vaccines in animals, and none have tested HSV-2 vaccines in HSV-1–seropositive animals. We used a guinea pig model of genital HSV-2 to evaluate the ability of vaccines to induce immunity and to protect against acute and recurrent HSV-2 disease. In one series of experiments, we compared HSV-2 dl5–29 with recombinant gD2 vaccines in 2 different adjuvants in HSV-1–seronegative guinea pigs; in another set of experiments, we compared these vaccines in HSV-1–seropositive guinea pigs.

METHODS

Viruses and vaccines. Replication-defective HSV-2 dl5–29 was described elsewhere [8, 9]. Recombinant glycoprotein D of HSV-2 (gD2) [10] was a gift from Chiron. Each animal received gD2 (3 µg) mixed with CFA or IFA (50 µL; Sigma-Aldrich) or absorbed to alum (75 µg; Inject Alum; Pierce) by mixing on a rotating wheel for 30 min at room temperature, followed by the addition of MPL (7.5 µg; Avanti Polar Lipids).

Guinea pig genital herpes model. All animal studies were approved by the Institutional Animal Care and Use Committee at the National Institute of Allergy and Infectious Diseases, National Institutes of Health (Bethesda, MD). For HSV-1–seropositive guinea pig experiments, 4–6-week-old female Hartley guinea pigs (Harlan Sprague Dawley) were infected with 1 × 10^6 of HSV-1 (strain KOS) intranasally; 7 weeks later, HSV-1 neutralizing antibody titers were measured. HSV-1–seropositive animals were immunized with phosphate-buffered saline (PBS) or gD2 intramuscularly in the thigh or with 1 × 10^4 pfu of HSV-2 dl5–29 subcutaneously on the back. Each vaccine was given on days 49 and 28 before intravaginal challenge with 1 × 10^6 or 4 × 10^6 of HSV-2 strain 333. A higher challenge dose of HSV-2 strain 333 was required in HSV-1–seropositive animals to induce genital herpes disease than for HSV-1–seronegative animals (unpublished data) as was expected, because HSV-1 has been shown to reduce symptomatic HSV-2 infection [6]. In preliminary experiments, HSV-1–seropositive animals did not develop genital herpes disease after challenge with the same dose of wild-type virus (2 × 10^5 pfu) that routinely causes disease in HSV-1–seronegative animals. We empirically found that increasing the dose of the challenge inoculum by 5–20-fold resulted in genital disease in most HSV-1–seropositive animals after challenge with wild-type HSV-2.

For HSV-1–seronegative animal experiments, 4–6-week-old female Hartley guinea pigs were vaccinated with the same vaccines described above and challenged intravaginally with 2 × 10^5 HSV-2 stain 333. Animals that died early after challenge were included in the analysis until their death and were then omitted from further analysis. Lesion severity after challenge was determined by direct examination of each animal daily for up to 60 days on the basis of a scale of 0 for no lesions, 1 for erythema, 2 for single or a few small vesicles, 3 for large or fused vesicles, and 4 for ulcerated lesions [7]. Animals were sacrificed after the last day of scoring and lumbosacral ganglia were stored at −20°C.

Neutralizing antibody responses, titration of virus shedding, and real-time PCR. Neutralizing antibody titers to HSV-2 strain 333 or HSV-1 strain KOS were quantified as described elsewhere [7]. Vaginal fluid specimens were collected after challenge, and HSV-2 titers were determined as previously described [7]. Animals that tested negative for shedding after challenge (1–3 animals from each group) were considered inadequately challenged and excluded from further analysis; these animals showed no change in HSV antibody titers after challenge (data not shown).

DNA from lumbosacral ganglia of individual latently infected guinea pigs was isolated using a SPrime, ArchivePure DNA isolation kit (Fischer Scientific Company). Latent HSV-2 DNA was quantified by real-time PCR using a Taqman System, 7500 Real-Time PCR System (Applied Biosystems) with primers and probes specific for HSV gD (which detect both HSV-1 and HSV-2 gD) [7] or HSV-1 gG [11]. For statistical purposes, reactions yielding <4 copies of HSV-2 DNA (the lower limit of detection of the assay) were assumed to contain 2 copies. The mean result for 3 independent experiments was determined.

Luciferase immunoprecipitation-assay system (LIPS). A LIPS assay [12] for quantifying antibody titers was described elsewhere [13]. In brief, Renilla luciferase–HSV-2 gB2, gD2, and ICP8 fusion proteins were harvested from transfected cell lysates and activity of lysates (in light units [LU] per milliliter) was determined by luminometry. Antibody titers were measured in LIPS assays by adding guinea pig serum to 1 × 10^5 LU of cell extract, immunoprecipitation was performed with addition of protein A/G beads, and the number of LUs was determined by luminometry. Background LU values were determined with serum specimens from 3 uninfected guinea pigs. A cut-off threshold limit was derived from the mean value plus 3 standard deviations of background LU for each HSV-2 antigen. All LU data shown represent the mean of 2 independent experiments after the cut-off threshold values have been subtracted out.
Statistical analysis. All statistical analysis was done using analysis of variance, and multiple comparisons were performed with the Student t test, unless otherwise indicated.

RESULTS

HSV-2 dl5–29 induces significantly higher neutralizing antibodies than does gD2 (CFA/IFA) or gD2 (alum/MPL) in guinea pigs, despite lower gD2-specific antibody responses. Serum neutralizing titers of HSV-1–seronegative guinea pigs receiving dl5–29 were significantly higher than those receiving gD2 (CFA/IFA) or gD2 (alum/MPL) (P < .01) (Figure 1A). Neutralizing titers in animals receiving gD2 (alum/MPL) were significantly higher than in those receiving gD2 (CFA/IFA) (P < .01). These results confirm our previous finding that dl5–29 induces higher neutralizing antibody titers than does gD2 (CFA/IFA) in guinea pigs.

Vaccination with dl5–29 induced anti-gB2, -gD2, and -gG2 antibodies but not anti-ICP8, which is deleted in dl5–29 (Figure 1B). Anti-gD2 titers were significantly higher in animals receiving gD2 (CFA/IFA) than in those receiving gD2 (alum/MPL) (P < .01), although HSV-2 neutralizing antibody titers were significantly higher with gD2 (alum/MPL) than gD2 (CFA/IFA) (P < .01) (Figure 1A). Anti-gD2 titers in animals receiving dl5–29 were significantly lower than those receiving gD2 (alum/MPL) or gD2 (CFA/IFA) (P < .01). HSV-2 neutralizing antibody titers showed a significant correlation with gD2-specific antibody titers in animals receiving gD2 (alum/MPL) (P < .01) but not in those receiving gD2 (CFA/IFA) (P = .45) or dl5–29 (P = .09) (Figure 1C). No correlation was seen for HSV-2 neutralizing antibody titers with gB2 antibody in animals receiving dl5–29 (data not shown). These data indicate that titers of gD2 antibody do not necessarily correlate with neutralizing antibody titers and that the contribution of individual viral proteins to the neutralizing antibody depends on the context of the vaccine and the adjuvant used.

HSV-2 dl5–29 reduces vaginal shedding in guinea pigs more effectively than gD2 (alum/MPL) or gD2 (CFA/IFA) after challenge with wild-type HSV-2. After challenge with wild-type HSV-2, titers of HSV-2 shed from the vaginal tract were consistently and significantly lower (P < .01) in animals vaccinated with dl5–29 than in those vaccinated with gD2 (alum/MPL) at all time points except for day 8, and titers were lower than for gD2 (CFA/IFA) on days 2 and 6 (Figure 2A). HSV-2 titers were significantly lower for dl5–29 than for PBS at all time points (P < .01). HSV-2 titers in animals receiving gD2 (alum/MPL) and gD2 (CFA/IFA) were similar. Thus, dl5–29 was the most effective vaccine at reducing HSV-2 vaginal shedding after challenge, whereas gD2 (alum/MPL) and gD2 (CFA/IFA) each had a modest effect.

Acute disease scores and numbers of recurrences after wild-type HSV-2 challenge in guinea pigs vaccinated with HSV-2 dl5–29, gD2 (alum/MPL), or gD2 (CFA/IFA). Animals vaccinated with dl5–29 had minimal disease scores during the first 2 weeks after challenge, whereas those vaccinated with gD2 (alum/MPL) or gD2 (CFA/IFA) had lower disease scores than

Figure. 1. Neutralizing and herpes simplex virus (HSV–2 antigen-specific antibody titers induced by vaccines in guinea pigs. A, Neutralizing antibody titers (50% plaque reduction) of serum samples from HSV-1–seronegative guinea pigs determined 3 weeks after the second vaccination. Each symbol represents an individual animal, short horizontal bars represent mean ± standard deviation for each group, vertical lines represent standard errors, and broken line indicates the limit of detection. Antibody titers were determined in 10, 12, 13, and 10 animals that received PBS (control), glycoprotein D (gD2) (complete Freund’s adjuvant followed by incomplete Freund’s adjuvant [CFA/IFA]), gD2 (alum/monophosphoryl lipid A [MPL]), and dl5–29, respectively. B, Anti-gB2, gD2, gG2, and HSV-2 ICPP antibody titers induced by the different vaccines (x-axis) before challenge assayed using the luciferase immunoprecipitation-assay system and antibody titers are shown in light units on the y-axis. Short horizontal bars on the x-axis indicate that no animal in the group showed a detectable antibody response. All titers shown have background activity (mean + 3 times the standard deviation of negative control serum) subtracted from the data shown. C, Correlation between anti-gD2 antibody titers induced by gD2 and dl5–29 vaccines (x-axis) and neutralizing antibody titers (y-axis). Lines in panel C indicate linear regression lines.
did those receiving PBS but higher disease scores than did those vaccinated with ds5–29 (Figure 2B). The acute disease scores for the vaccinated groups (P < .01, P = .04, and P = .04 for ds5–29, gD2 [CFA/IFA], and gD2 [alum/MPL], respectively) were significantly lower than that for the PBS group, but they were not significantly different from each other. Animals vaccinated with ds5–29 had fewer numbers of recurrences than did those receiving gD2 [CFA/IFA] or gD2 [alum/MPL] (Figure 2C). The differences between the ds5–29 and gD2 [CFA/IFA] or gD2 [alum/MPL] groups were not significant.

The latent viral load of guinea pigs vaccinated with HSV-2 ds5–29 is significantly lower than in those vaccinated with gD2 (alum/MPL) or gD2 [CFA/IFA] after challenge with HSV-2. The latent viral load of HSV-2 in sacral ganglia of animals vaccinated with ds5–29 was significantly lower than that of other groups (P < .03) (Figure 2D). The latent viral loads were not significantly different among PBS, gD2 [CFA/IFA], and gD2 (alum/MPL) groups. In the present experiment, 77% of animals in the PBS control group died after HSV-2 challenge, whereas 23% died in prior experiments (P < .01, for PBS vs any vaccine group; data not shown) [7]. Although the dose of challenge virus was the same in both experiments, animals were from a different supplier and had lower body weights in the present experiment. Because only 3 animals survived in the PBS group, the statistical power for comparison between this group and the other groups was low.

Antibody responses against HSV-2 gB, gD, gG, and ICP8 were detected in all vaccine groups after challenge using the LIPS assay (data not shown). Anti-gD2 antibody titers increased in all vaccine groups, including gD2 vaccine recipients, after challenge. Antibody titers to gB2, gG2, and ICP8 (absent in ds5–29) were also increased in ds5–29 group after challenge, even though these animals showed minimal acute and recurrent disease. Antibody to ICP8 was detected in some animals that received ds5–29 (which is deleted for this protein) after challenge; however, the titer of ICP8 antibody was low in animals receiving ds5–29, which mirrored the mild acute and recurrent disease in these animals after challenge.
Analysis of antibody titers after vaccination—but before challenge—showed that the level of HSV-2 neutralizing titers or gD2 titers did not correlate with severity of acute disease, shedding, numbers of recurrences, or latent viral loads in animals receiving the gD2 vaccines (data not shown), suggesting that neutralizing antibody alone is insufficient for protection from HSV-2 genital disease.

Neutralizing titers against HSV-2 are similar in HSV-1-seropositive animals vaccinated with HSV-2 d15–29, gD2 (CFA/IFA), and gD2 (alum/MPL). Guinea pigs were infected with HSV-1, virus neutralizing antibody titers were determined in each animal, and the animals were divided into 3 groups so that levels of HSV-1 neutralizing antibody titers would be similar for subsequent vaccine studies (Figure 3A). HSV-1 neutralizing antibody titers were significantly increased after vaccination with gD2 (CFA/IFA), gD2 (alum/MPL), or d15–29, compared with the titers before vaccination (P<.01 for each group for before vs after vaccination) (Figure 3A). HSV-1 neutralizing antibody titers in the PBS group were similar before and after vaccination. HSV-1 neutralizing titers in animals vaccinated with each of the 3 vaccines were significantly higher than in those that received PBS (P<.02), whereas the HSV-1 neutralizing titers did not significantly differ between the vaccine groups (Figure 3A). Therefore, the 3 vaccines boosted anti-HSV-1 neutralizing antibody titers to similar levels.

HSV-2 neutralizing antibody titers in animals vaccinated with d15–29 were not significantly different from those in animals vaccinated with gD2 (CFA/IFA) or gD2 (alum/MPL) (Figure 3B). HSV-2 neutralizing titers in HSV-1-seropositive guinea pigs in the PBS group were significantly lower than those in the d15–29, gD2 (CFA/IFA), and gD2 (alum/MPL) groups (P<.01).

HSV-2 d15–29 reduces vaginal shedding after challenge in HSV-1-seropositive guinea pigs more effectively than does gD2 (CFA/IFA) or gD2 (MPL/alum). HSV-1-seropositive guinea pigs were vaccinated twice and then challenged with wild-type HSV-2 intravaginally (1 × 10⁴ or 4 × 10⁴ pfu for the left and right panel, respectively, in Figure 4A). Titers of HSV-2 shed from animals vaccinated with d15–29 or gD2 (alum/MPL) were significantly lower than in those that received PBS on days 2, 4, and 6 (P<.01) but not day 8 after challenge. Titers of HSV-2 in the gD2 (CFA/IFA) group were significantly lower than that of the PBS only on day 2 (P<.01) but not on days 4, 6, or 8. Differences in HSV-2 shedding between animals vaccinated with d15–29 and gD2 (alum/MPL) were significant on day 2 (P<.01) but not on days 4, 6, or 8. Titers of HSV-2 shed from animals receiving d15–29 were significantly lower than those of gD2 (CFA/IFA) on day 4 and 6 (P<.01) but not on days 2 and 8. Therefore, animals vaccinated with d15–29 had the lowest levels of HSV-2 shedding after challenge, whereas those vaccinated with gD2 (alum/MPL) had the next-lowest levels.

HSV-2 d15–29, gD2 (CFA/IFA), and gD2 (alum/MPL) protect HSV-1-seropositive guinea pigs from acute and recurrent disease after challenge. Acute disease scores for HSV-1-seropositive animals were significantly lower in the d15–29, gD2 (CFA/IFA), and gD2 (alum/MPL) groups than in the PBS group (P<.01), and the differences between the d15–29, gD2 (CFA/IFA), and gD2 (alum/MPL) groups were not significant (Figure 4B). The mean number of cumulative recurrences was significantly lower for animals vaccinated with d15–29, gD2 (CFA/IFA), or gD2 (alum/MPL) than for those vaccinated with PBS (P<
Animals vaccinated with d5–29 had fewer recurrences than those receiving gD2 (CFA/IFA) or gD2 (alum/MPL), but the differences were not significant (Figure 5A and 5B) because of the low reactivation rates in the gD2 recipients.

**HSV-2 d5–29 and gD2 (alum/MPL) significantly reduce the HSV latent viral load in HSV-1–seropositive guinea pigs.**

The latent viral loads in animals vaccinated with d5–29 were significantly lower than those receiving PBS (P < .01) (Figure 5C and 5D). The latent viral loads in the gD2 (CFA/IFA) and PBS groups were similar, but the difference between gD2 (CFA/IFA) and d5–29 was statistically significant (P = .043) (Figure 5C). The latent viral load in animals receiving gD2 (alum/MPL) was significantly lower than that in animals receiving PBS (P < .01) (Figure 5D), while the latent viral load of the d5–29 and gD2 (alum/MPL) groups were similar. Animals were challenged with 4-fold higher titers of wild-type HSV-2 in the experiment with gD2 (alum/MPL) than animals in the experiment with gD2 (CFA/IFA), which is reflected in the higher latent viral load in the PBS group in Figure 5D than that of the PBS group.
in Figure 5C. Therefore, the low latent viral loads of dl5–29 and gD2 (alum/MPL) suggest that these vaccines were especially effective in reducing the viral load.

**DISCUSSION**

We have shown that, in HSV-1–seronegative guinea pigs, dl5–29 induces higher titers of HSV-2 neutralizing antibodies than does gD2 (alum/MPL) or gD2 (CFA/IFA) and that dl5–29 results in lower rates of virus shedding, lower latent viral loads in ganglia, and a tendency for less acute and recurrent genital herpes disease, compared with gD2 (alum/MPL) or gD2 (CFA/IFA), after challenge with wild-type virus. In HSV-1–seropositive guinea pigs, all 3 vaccines showed similar titers of HSV-2 neutralizing antibody and equivalent protection against acute and recurrent HSV-2 disease after challenge; however, dl5–29 resulted in the lowest virus shedding, and dl5–29 and gD2 (alum/MPL) significantly reduced the latent viral load. Detection of antibody to HSV ICP8, albeit at low titers in animals that received dl5–29, suggests that this antibody might be useful as a marker of infection if such a vaccine was used in humans. We have previously shown that antibody to ICP8 can readily be detected in HSV-2 seropositive humans [13].

To date, all animal studies of genital herpes vaccines have involved HSV-1–seronegative animals. We found that gD2 in alum/MPL (as well as gD2 [CFA/IFA] and dl5–29) was effective in protecting HSV-1–seropositive female guinea pigs, indicating that the animal model did not recapitulate the lack of efficacy of gD2 in alum/MPL observed in HSV-1–seropositive women. Several features of the model might explain the differences in the animal and human studies. First, guinea pigs were vaccinated 2–3 months after HSV-1 infection, whereas in the clinical trial, the interval between HSV-1 infection and vaccination was many years. Immune responses are known to mature after infection with an increasing avidity [14], and the long period between HSV-1 infection and vaccination in the clinical trial may have favored better protection to HSV-2. Second, the interval between vaccination and HSV-2 infection was shorter in the animal experiments than in the clinical trial. In a clinical trial of gD2 and gB2 in MF59 adjuvant, although the vaccine was not effective during the 1-year follow-up period, there was a lower rate of genital herpes during the first 5 months after vaccination [3]. Third, the challenge dose of wild-type virus might be higher in animal experiments, in which nearly all the animals are infected with the challenge dose, than after natural infection of humans. Cross-protection against HSV-2 in HSV-1–seropositive animals might be insufficient to protect animals from a high titer HSV-2 challenge, whereas it might protect humans from a low titer virus challenge and mask the efficacy of an HSV-2 vaccine.

We also compared gD2 in 2 different adjuvants, CFA/IFA and alum/MPL, for their ability to protect HSV-1–seronegative guinea pigs. Rupp et al [15] reviewed human trials of gD2 vaccines and noted that gD2 and gB2 in MP59 adjuvant [3] induced higher levels of neutralizing antibody, whereas gD2 in alum/MPL [4] induced higher Th-1 cell–mediated immune responses. Bourne et al [16] compared guinea pigs vaccinated with gD2 in alum versus gD2 in alum/MPL and found that the both provided similar protection against acute disease after intravaginal challenge with HSV-2, but that gD2 in alum/MPL provided better protection against recurrent disease than did gD2 in alum. Berman et al [17] vaccinated guinea pigs with gD1 in CFA or alum and challenged the animals with HSV-2 by intravaginal infection; animals receiving gD2 in CFA were protected from acute genital disease, whereas those receiving gD2 in alum were only partially protected. Sanchez-Pescador et al [18] compared guinea pigs immunized with gD1 in CFA and alum and found that gD1 in CFA resulted in lower acute disease scores than gD1 in alum after intravaginal challenge with HSV-2. We performed, to our knowledge, the first comparison of gD2 in alum/MPL versus gD2 in CFA and found that gD2 (alum/MPL) was as effective as gD2 (CFA/IFA) in protecting HSV-1–seronegative or seropositive guinea pigs from acute and recurrent HSV-2 infection.

We found that dl5–29 significantly reduced the latent viral load, compared with gD2 (CFA/IFA) or gD2 (alum/MPL), in HSV-1–seronegative guinea pigs after challenge with HSV-2 and that dl5–29–vaccinated animals had a reduced acute and recurrent genital herpes disease (but this did not reach statistical significance). In our prior experiments [7], there was no significant difference in the latent viral load in HSV-1–seronegative guinea pigs receiving dl5–29 and gD2 in CFA/IFA, and the difference in acute and recurrent genital herpes disease was less apparent in the 2 vaccines. Although the dose of challenge virus was the same, in the current experiment, more animals died in control group. Thus, dl5–29 may be more effective than the gD2 vaccines at effectively higher challenge inocula.

We found that neutralizing antibody titers prior to challenge did not correlate with reduced severity of acute or recurrent disease in animals that received the gD2 vaccines, indicating that other factors besides—or in addition to—neutralizing antibodies are important for protection against HSV-2 disease. Although both antibody and cellular immunity are important, the true immunologic correlates of protection from HSV-2 genital disease are not known [19]; therefore, animal studies continue to be important for testing vaccines. In human trials, the gender and HSV-1 serostatus of vaccine recipients have been important determinants for vaccine efficacy. Because ≥50% of adults are HSV-1 seropositive, and because the immune response to HSV-1 affords some level of cross-protection from HSV-2 disease, future studies of HSV-2 vaccines need to be performed in HSV-1–seropositive animals. Our experiments have shown that dl5–29 is an effective candidate vaccine in
both HSV-1–seronegative and HSV-1–seropositive guinea pigs and that dIL–29 reduces vaginal shedding significantly better than gD2 vaccines in both HSV-1–seronegative and HSV-1–seropositive guinea pigs. Mathematical modeling suggests that reduced shedding of HSV-2 by vaccination may have a substantial impact at the population level by limiting transmission of genital herpes [20]. Thus, these studies indicate that dIL–29 represents an excellent candidate HSV-2 vaccine candidate for clinical trials in humans.

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References