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

Yo Hoshino,1 Lesley Pesnicak,1 Kennichi C. Dowdell,1 Peter D. Burbelo,2 David M. Knipe,3 Stephen E. Straus,1 and Jeffrey I. Cohen1

1Medical Virology Section, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, and 2Neurobiology and Pain Therapeutics Section, Laboratory of Sensory Biology, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, Maryland; and 3Department of Microbiology and Molecular Genetics, Harvard Medical School, Boston, Massachusetts

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–seronegative 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 vaccines. 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]. Stanford 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 or 61 × 10^6 of HSV-2 strain 333. A higher challenge dose of 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.
**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/GPL) 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 (aluum/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...
The latent viral loads of HSV-2 in sacral ganglia of animals vaccinated with gD2 (CFA/IFA), or gD2 (alum/MPL) were significantly lower than that for the PBS group, but they were not significantly different from each other. Animals vaccinated with gD2 (alum/MPL), and gD5–29, respectively. Five animals did not become infected after challenge (2 had received PBS, 1 had received gD2 [alum/MPL], and 2 had received gD5–29). Acute disease scores for the 3 vaccinated groups. Scores were significantly lower for the 3 vaccinated groups, compared with the PBS group (P < .05). The number of recurrences was significantly lower for animals vaccinated with gD5–29 or gD2 [alum/MPL] than for those that received PBS (P < .01 for gD5–29 vs PBS; P < .05 for gD2 [alum/MPL] vs PBS); the number of recurrences for animals vaccinated with gD2 [CFA/IFA] was not significantly lower than for those that received PBS (P = .09). D, Latent HSV-2 load in pooled sacral ganglia (SG) after challenge with wild-type virus. Each symbol indicates individual animals from the same group. Vertical bars indicate standard errors. The broken line indicates the limit of detection. The number of animals surviving and analyzed for latent viral DNA was 3, 10, 12, and 8 for PBS (control), gD2 [CFA/IFA], gD2 [alum/MPL], and gD5–29, respectively.

**Figure 2.** Vaccination of herpes simplex virus (HSV)-1–seronegative guinea pigs with d5–29, glycoprotein D (gD2; complete Freund’s adjuvant [CFA/IFA]), gD2 [alum/monophosphoryl lipid A [MPL]], or PBS. Animals were vaccinated twice with either PBS (control), gD2 [CFA/IFA], gD2 [alum/MPL], or d5–29 separated by a 3-week interval and challenged with wild-type HSV-2 intravaginally at 3 weeks after the second vaccination. A, HSV-2 shedding from the vaginal tract on days 2, 4, 6, and 8 after challenge with wild-type HSV-2. Titers of HSV-2 were not different for PBS versus gD2 [alum/MPL] or versus gD2 [CFA/IFA] on days 2, 4, and 6 (P > .15) and were not different for gD2 [alum/MPL] versus gD2 [CFA/IFA] at any time point (P > .15). The number of animals vaccinated that shed virus after challenge was 13, 12, 12, 8, for PBS (control), gD2 [CFA/IFA], gD2 [alum/MPL], and gD5–29, respectively. Five animals did not become infected after challenge (2 had received PBS, 1 had received gD2 [alum/MPL], and 2 had received gD5–29). B, Acute disease scores for the 3 vaccinated groups. Scores were significantly lower for the 3 vaccinated groups, compared with the PBS group (P < .05). C, Cumulative number of recurrences in animals vaccinated with gD5–29 or gD2 [alum/MPL]. The number of recurrences were significantly lower for animals vaccinated with gD5–29 or gD2 [alum/MPL] or versus gD2 [CFA/IFA] or between gD2 [alum/MPL] and gD (CFA/IFA) not significant (P > .08). D, Latent HSV-2 load in pooled sacral ganglia (SG) after challenge with wild-type virus. Each symbol indicates individual animals from the same group. Vertical bars indicate standard errors. The broken line indicates the limit of detection. The number of animals surviving and analyzed for latent viral DNA was 3, 10, 12, and 8 for PBS (control), gD2 [CFA/IFA], gD2 [alum/MPL], and gD5–29, respectively.

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 were increased in all vaccine groups, including gD2 vaccine recipients, after challenge. Antibody titers to gB2, gG2, and ICP8 (absent in d5–29) were also increased in d5–29 group after challenge, even though these animals showed minimal acute and recurrent disease. Antibody to ICP8 was detected in some animals that received d5–29 (which is deleted for this protein) after challenge; however, the titer of ICP8 antibody was low in animals receiving d5–29, 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 dl5–29, 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 dl5-29, 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 dl5–29 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 dl5–29, gD2 (CFA/IFA), and gD2 (alum/MPL) groups (P<.01).

HSV-2 dl5–29 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 × 10^6 or 4 × 10^6 pfu for the left and right panel, respectively, in Figure 4A). Titers of HSV-2 shed from animals vaccinated with dl5–29 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. The differences in HSV-2 shedding between animals vaccinated with dl5–29 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 dl5–29 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 dl5–29 had the lowest levels of HSV-2 shedding after challenge, whereas those vaccinated with gD2 (alum/MPL) had the next-lowest levels.

HSV-2 dl5–29, 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 dl5–29, gD2 (CFA/IFA), and gD2 (alum/MPL) groups than in the PBS group (P<.01), and the differences between the dl5–29, 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 dl5–29, gD2 (CFA/IFA), or gD2 (alum/MPL) than for those vaccinated with PBS (P<
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Figure 4. Shedding of herpes simplex virus (HSV)-2 and acute disease scores in HSV-1–seropositive guinea pigs vaccinated with dl5–29, glycoprotein D (gD2; complete Freund’s adjuvant followed by incomplete Freund’s adjuvant [CFA/IFA]), and gD2 (alum/monophosphoryl lipid A [MPL]). A, Geometric mean titers of HSV-2 shed from the vaginal tract on days 2, 4, 6, and 8 for animals vaccinated with dl5–29, gD2 (CFA/IFA), or PBS (left panel) and animals vaccinated with dl5–29, gD2 (alum/MPL), or PBS (right panel). Vertical bars indicate standard errors, and broken lines indicate the limit of detection. B, Group mean lesion scores for acute infection in animals vaccinated with dl5–29, gD2 (CFA/IFA), or PBS (left panel) and animals vaccinated with dl5–29, gD2 (alum/MPL), or PBS (right panel). The number of animals analyzed for shedding and acute disease was 26, 18, and 18 for PBS (control), gD2 (CFA/IFA), and dl5–29, respectively (left panels in A and B) and 23, 16, and 16 for PBS (control), gD2 (alum/MPL), and dl5–29, respectively (right panels in A and B). One animal (in the PBS group in the left panels) did not become infected after challenge.

Figure 5. Cumulative number of recurrences and latent viral loads in herpes simplex virus (HSV)-1–seropositive animals vaccinated with dl5–29, glycoprotein D (gD2; complete Freund’s adjuvant followed by incomplete Freund’s adjuvant [CFA/IFA]), and gD2 (alum/monophosphoryl lipid A [MPL]). A, Cumulative numbers of recurrences in animals vaccinated with PBS ( ), gD2 (CFA/IFA; ), or dl5–29 ( ) and in animals vaccinated with PBS ( ), gD2 (alum/MPL; ), or dl5–29 ( ) (A). Latent HSV-2 loads in sacral ganglia (SG) in animals were analyzed in animals vaccinated with PBS ( ), gD2 (CFA/IFA) ( ), or dl5–29 ( ) and in animals vaccinated with PBS ( ), gD2 (alum/MPL) ( ), or dl5–29 ( ) (B). Each symbol indicates individual animals from the same group. Horizontal bars indicate mean ± standard deviation, and the broken line indicates the limit of detection.

Animals vaccinated with dl5–29 had fewer recurrences than did 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 dl5–29 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 dl5–29 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 dl5–29 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 dl5–29 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.
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–seropositive 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–seropositive 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–seropositive 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.
both HSV-1-seronegative and HSV-1-seropositive guinea pigs and that dl5–29 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 dl5–29 represents an excellent candidate HSV-2 vaccine candidate for clinical trials in humans.

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References