Vaccine	Vaccine quantity, route and schedule	Results post challenge	Ref
Replication-competent			
HSV-1 with deletion of thymidine kinase gene, replaced with HSV-2 gD, gG, gI, and gE (R7017)	10^8 PFU ID or IM	Decreased proportion of animals with vaginal shedding and genital lesions, and decreased lesion severity and death after ivag challenge. Challenge strain recovered from DRG after both ID and IM vaccination.	(131)
HSV-1 with deletion of thymidine kinase gene, replaced with HSV-2 gD, gG, gI, and gE, plus thymidine kinase gene (R7020)	10^8 PFU ID or IM	Decreased proportion of animals with vaginal shedding and genital lesions, decreased lesion severity and death after ivag challenge, compared with control. Challenge strain recovered from DRG after both ID and IM vaccination.	(131)
HSV-2 strain G with deletion of $\gamma_1$34.5 and UL55-56 (RAV 9395)	$1x10^4$-5 x 10^6 PFU IM	No change in proportion of animals with vaginal shedding post challenge, but decreased viral titer in highest vaccine dose group. Decreased development and severity of lesions. Challenge strain recovered from DRG in 3 of 12 animals who received $1x10^6$ PFU vaccine strain and 0 of 6 animals who received 5 x 10^6 PFU	(132)
HSV-2 strain G with deletion of $\gamma_1$34.5, UL55-56, UL43.5, US10-12 (AD-472)	10^3 or 10^5 PFU IM	Reduction in lesion days and peak lesion scores. Latent virus recovered from 3 (60%) of 5 animals who received low dose vaccine and high dose challenge, and from 1 of 5 (20%) who received high dose vaccine and high dose challenge.	(41)
HSV-2 mutant strain with deletion in UL39 (ICP10(ΔPK))	10^6 PFU SC x 2	Decreased proportion of animals with genital lesions (1 (10%) of 10 vs. 10 /10 control), decreased lesion severity post vaccination. Did not test for presence of latent virus in DRG post challenge.	(133)
Replication-incompetent			
HSV-1 with deletion of gH gene (Disabled infectious single-cycle (DISC) virus)	2 x 10^7 PFU intraepithelial, ivag	Decreased number of lesions and erythema, decreased duration of lesions. Ivag prep more effective than intraepithelial. Decreased recurrent disease post vaccination (60% reduction in days with lesions ivag vaccine group). However, recurrences occurred in all vaccinated animals.	(134)
HSV-2 (HG52) with deletion of gH gene (Disabled infectious single-cycle (DISC) virus)	10^6 or 10^7 PFU SC or ivag x 2	SC vaccination associated with complete protection from primary disease, ivag vaccination reduced lesions by 85% (low dose) and 92% (high dose), decreased titer of challenge virus post vaccination. 2 of 24 vaccinated animals had recurrent lesions (98% reduction compared to mock vaccinated) post challenge.	(135)
HSV-2 with mutation in ICP8/UL29	10^7 PFU SC, ivag	Decreased proportion of animals developed primary disease (9 (38%) of 24 vs. 11 (92%) of controls, with decreased lesion severity and decreased quantity and duration of viral shedding, and decreased frequency of recurrences.	(136)
HSV-2 strain 186, with deletion in UL5 and UL29 (dl5-29)	10^6 PFU SC, ivag x 2	Dl5-29 completely prevented acute genital disease and decreased vaginal shedding after challenge. Latent virus present in 5 of 10 animals post vaccination, quantity of latent virus similar to controls.	(113, 137)
HSV-2 strain 186, with deletion UL5, Ul29, and lacZ inserted in place of UL41 (dl5-29-41L)	10^6 PFU SC, ivag x 2	Decreased lesion scores and reduced quantity of vaginal shedding. Cumulative decrease in number of recurrences over 90 days post challenge (3 vs. 15 in control animals). Decreased quantity of virus detected in DRG post vaccination as compared to control. Dl5-29 and dl5-29-41L equally effective.	(89)
Recombinant HSV-1, dominant-negative mutation in UL9 with extra copy of gD1 gene (CF9-D9)	5 x 10^6 PFU SC x 2	Decreased incidence of lesions and decreased severity of lesions, and reduction in quantity and duration of viral shedding. No lesions or recurrent shedding among immunized animals over 60 days follow up, 50-fold reduction in quantity of virus detected in DRG.	(112)

Supplemental Table 1

Live-virus vector			
rOka VZV expressing HSV-2 glycoprotein gD2	3.2 x 10^4 $TCID_{50}$ rOka VZV-gD2 IM x 3	All immunized animals developed skin lesions, however, severity was reduced compared with controls. Quantity of vaginal shedding during primary infection similar between immunized and control animals. All immunized animals developed recurrent disease.	(138)
Recombinant vaccinia virus expressing gD2	1 x 10^7 PFU vaccinia-gD2 ivag, IN, ID x 2	Animals who received ivag vaccine had decreased incidence of primary disease and decreased recurrences. All vaccinated animals had decrease in total lesion score. Vaginal titers reduced for all immunized groups, with lowest titers found in intravaginal vaccination group.	(139)
Recombinant vesicular stomatitis virus vector expressing HSV-2 glycoprotein gD2 (rVSV-gD)	10^3-10^7 PFU IN x 2	Complete protection against genital lesions post challenge in animals immunized with ≥10^4 PFU. At 10^7 PFU, 1 of 10 guinea pigs had HSV detected in DRG, with marked decrease in copy number detected.	(140)
DNA			
Full length gD2	50-250 µg DNA IM x 3	Decreased incidence and severity of primary disease. Frequency of viral shedding was not decreased in immunized animals, but quantity of virus shed was lower. Reduced incidence and frequency of recurrent disease. 29 of 29 immunized guinea pigs had HSV DNA detected in DRG, but decrease in quantity of virus detected.	(141)
Full length gD2 and truncated gB2 or truncated gB2 alone	10-200 µl DNA IM x 2	Decreased lesion scores, decreased overall severity of primary infection. Significantly fewer recurrences over 5-week period	(142)
Full length gB2 or gC2	100 µg DNA IM x 2-3	Decreased lesion scores and recurrences in animals who received gB2 but no difference in viral titers post challenge, no protection from gC2 DNA	(143)
Full length gD2 DNA-prime protein boost (expressed in baculovirus system)	100 µg DNA IM +/- gD2 protein boost at day 14	Decreased lesion scores and severity of infection post challenge in all immunized groups. Decreased quantity of vaginal shedding, but all vaccinated animals shed post challenge.	(144)
DNA prime (gD2 truncated, + UL5 and UL30 or UL29 and UL52) followed by formalin-inactivated HSV-2 with MPL/alum adjuvant boost	100 µg DNA ID x 3 + 2 x 10^7 FI-HSV-2 SC boost after 6 weeks, x 2	Decreased rates of acute lesion development; no significant difference between vaccines. No differences in quantity of virus shed, significant decrease in proportion of animals shedding compared to mock. All vaccine groups had lower rates of recurrence over 100 days follow up and lower quantity of HSV-2 detected in DRG	(145)
Glycoprotein based vaccine			
Recombinant carboxytruncated gD2 with MF59 (IM) or LTK63 (intranasal) adjuvant	100 µg gD2 IN or 25 µg gD2 IM x 3	Reduced incidence of disease, mean lesion score and severity in animals who received gD2 + MF59 IM. In animals who received gD2 + LTK63 IN, no reduction in incidence of disease, but decreased average lesion score and reduced mortality.	(146)
HSV-1 glycoproteins preparation forumulated with immunostimulatory complex (Iscom) system or Alum	20 µg protein SC x 2	Decreased mean lesion score with either adjuvant. No change in quantity of viral shedding post challenge. Reduced recurrences post challenge in animals immunized with Iscom adjuvant, but recurrences not prevented. No significant decrease in recurrences for animals who received alum adjuvant	(147)
Recombinant carboxytrunctated gD2, with alum or AS04 adjuvant	5 µg gD2 SC x 3	Decreased incidence and severity of genital disease post challenge. Over 42 day period, significant reduction in incidence of recurrences in gD2/AS04 immunized animals.	(148)

Supplemental Table 1

Recombinant carboxytrunctated gD2, with alum or AS04 adjuvant	5 µg gD2 IM x 2	Complete protection against primary disease. Decreased incidence and frequency of recurrent lesions. Shedding rate was unchanged, but quantity of virus shed decreased in vaccinated animals. All immunized animals had virus detected in DRG, decreased quantity of viral DNA in DRG of immunized animals	(96)
Recombinant glycosylated external domain of gD1, alone or with GPI-0100 +/- Tween 40 adjuvant	20 µg gD1 IM x 3	Decreased AUC lesion day in all immunized animals. Decreased lesion scores only in animals receiving gD1+GPI-0100+Tween 40. No difference in number or length of recurrences for any immunized animals compared to placebo.	(149)
Recombinant gD2 truncated at transmembrane domain alone or with cationic liposome DNA complex (CDLC) or MPL/alum adjuvant	5 µg gD2 SC x 2	Animals vaccinated with gD2 + CLDC had decreased disease post challenge compared to other vaccinated groups. Decreased quantity of virus shed in both gD2 + CLDC and gD2 + MPL/Alum groups compared to gD2 alone. Fewest recurrences in gD2 + CLDC group (1 of 12 animals vs 6 of 12 in gD2 + MPL/Alum group) and shedding days, and reduced proportion of animals with HSV detected in DRG.	(150)
Recombinant gD2, soluble gD2 +/- soluble gB2 + soluble truncated gH2/gL2 complex, with CLDC adjuvant	SC x 2	All vaccinated animals had decreased incidence and severity of disease and vaginal virus replication at day 2 and 5. Number of days with recurrence decreased in all vaccinated animals. No difference in shedding rate between animals receiving vaccine and placebo. Decreased number of animals with virus detected in DRG (75% in placebo, 17-42% in vaccine groups).	(97)

Supplemental Table 1. Prophylactic vaccines tested using the intravaginal challenge guinea pig model.

Note: Initial glycoprotein vaccines (1985-1995) excluded from table due to space limitations.. AS04=alum and 3-deactylated monophosphoryl lipid A (3-dMPL). PFU=plaque forming units, SC=subcutaneous, IM=intramuscular, IN=intranasal, ivag=intravaginal, ID=intradermal