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Herpes simplex virus

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450Mic – Medical Virology

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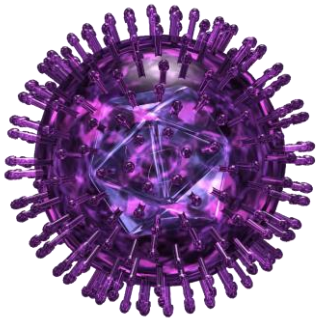
Introduction:

Herpes simplex viruses (HSV) more commonly known as herpes are categorized into two types: herpes type 1 (HSV-1, or oral herpes) and herpes type 2 (HSV-2, or genital herpes). Most commonly, herpes type 1 causes sores around the mouth and lips (sometimes called fever blisters or cold sores). HSV-1 can cause genital herpes, but most cases of genital herpes are caused by herpes type 2. In HSV-2, the infected person may have sores around the genitals or rectum. Although HSV-2 sores may occur in other locations, these sores usually are found below the waist. (1)

Herpes simplex viruses are recognized since ancient Greek times . HSV are among the most ubiquitous of human infections. The frequency of HSV infection has been measured by testing various populations for the presence of antibody, as both virus and the immune response are thought to persist after infection for the life of the host. Worldwide, ˜ 90% of people have one or both viruses. HSV-1 is the more prevalent virus, with 65% of persons in the United States having antibodies to HSV-1

(Xuet al., 2002).

The HSV-1 prevalence rates increase minimally with age. Rates of HSV-1 infection are similar for men and women. In the United States, African-Americans and Asians have higher rates of HSV-1 infection than whites. The majority of infections are oral, although most are asymptomatic. Some data suggest that in developed countries, acquisition of HSV-1 is delayed from early childhood to adolescence or young adulthood



(Mertz et al., 2003).

Genital herpes caused by HSV-2 is a global issue, and an estimated 417 million people worldwide were living with the infection in 2012. Prevalence of HSV-2 infection was estimated to be highest in Africa (31.5%), followed by the Americas (14.4%). It was also shown to increase with age, though the highest numbers of people newly-infected were adolescents. (2)

More women are infected with HSV-2 than men; in 2012 it was estimated that 267 million women and 150 million men were living with the infection. This is because sexual transmission of HSV is more efficient from men to women than from women to men. (2)

Classification:

Order: Group I (dsDNA)

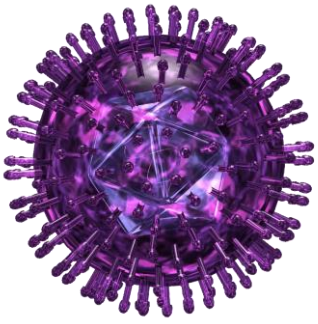
Family: Herpesviridae

Subfamily: Alphaherpesvirinae

Genus: Simplexvirus

Species: Herpes simplex virus 1 (HSV-1)

Herpes simplex virus 2 (HSV-2) (3)



Structure and genome:

HSV-1 and HSV-2 contain a large double-stranded DNA linear molecule.

The HSV virion has four parts: an electrondense core containing viral DNA; an icosapentahedral capsid; a tegument— an amorphous layer of proteins that surround the capsid; and an envelope.

with virions ranging from 120 nm (nanometres) to 300 nm in size

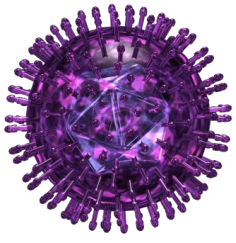
Genome size 125 kbp, long and short fragments with a total of 4 isometric forms .

The DNA of HSV-1 and HSV-2 consists of two covalently linked components, L (long) and S (short), with unique sequences—UL (unique long) or US (unique short flanked by large inverted repeats.

(Richard et al,2001)

The tegument is located between the capsid and the envelope and various proteins that are delivered into the infected cell upon cell fusion.

It contains three main structural components. A central core holds the viral DNA, an inner core is surrounded by an envelope that is made of viral glycoproteins and host cell membranes, and a capsid. (4)



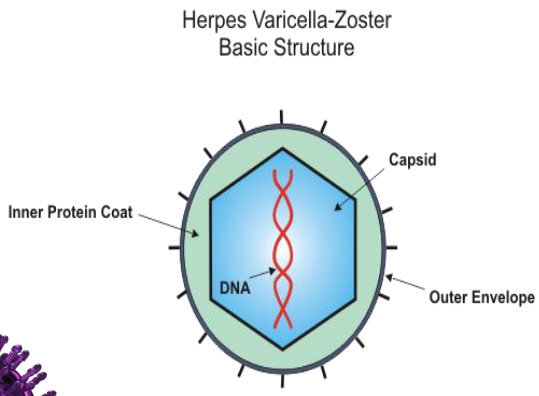


Figure (1)

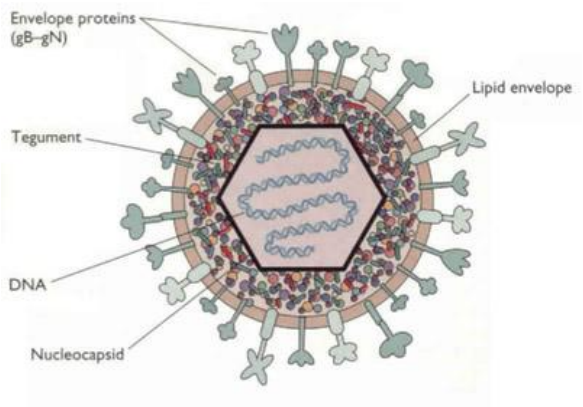


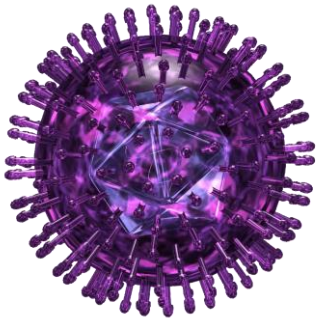
Figure (2)

Virulence factors:

There are about 40 to 50 different proteins in the virion ("virion structural proteins"). Some of these proteins make up the icosahedral capsid, some make up the tegumet, and some are the glycoproteins in the envelope,When the virus is attached, the viral envelope will fuse with the cellular membrane, leading to the release of proteins from the tegument and from the nucleocapsid into the cytoplasm the viral genome is rapidly circularized in the absence of any viral protein synthesis suggesting a mechanism under dependence of cellular proteins and/or structural viral proteins. The transcription of the herpesviruses' genome then proceeds.

(Thomas C. Mettenleiter,2002).

Following a series of events that are strictly regulated by viral proteins. We can distinguish three transcriptional phases. The first wave of transcription is initiated by the regulatory tegument proteins and allows the transcription of genes called "immediate-early" (IE) or α. The proteins synthesized at this stage essentially act as activators of transcription. Subsequently, the genes "early" (E) or β including the viral DNA polymerase, are transcribed. The last phase, called late (L) or γ, allows the synthesis of structural proteins including the envelope glycoproteins and the capsid proteins. Protein synthesis occurs in the cytoplasm and some of these proteins are then imported into the nucleus to stimulate transcription of E and L genes, but also to inhibit the transcription of IE genes.



These steps are explained in the following picture :

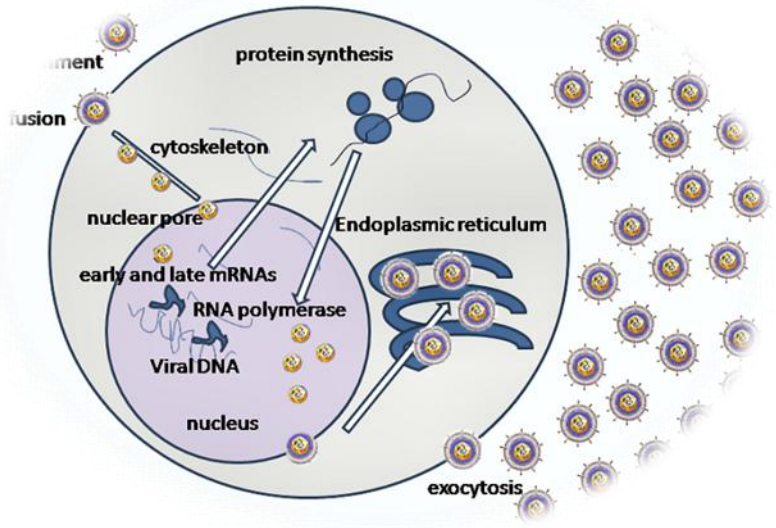


Figure (3)

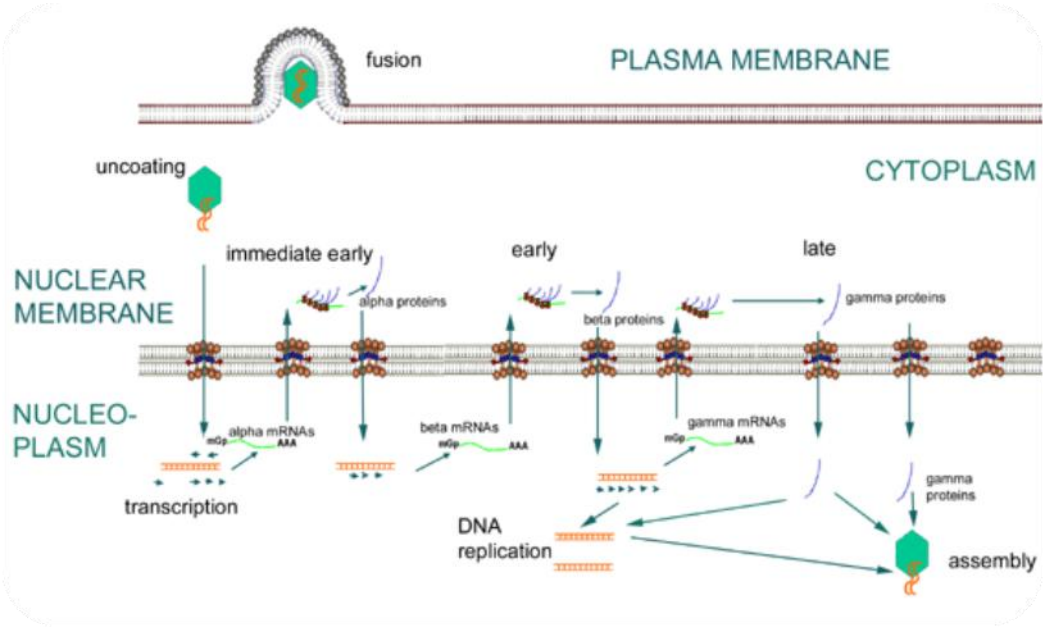
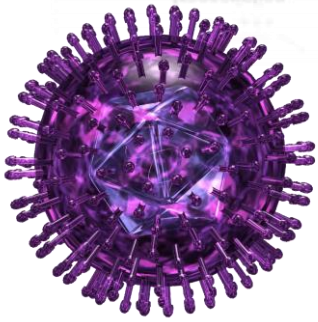


Figure (4)



Some of protein are shown in the following table :

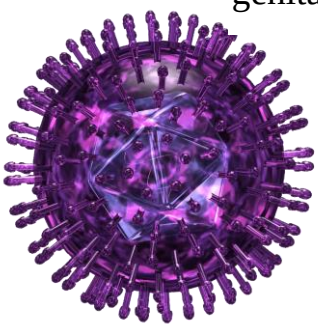
Protein	Function/description
Glycoprotein L	**Surface and membrane**
UL38; VP19C	**Capsid assembly and DNA maturation**
Glycoprotein C	**Surface and membrane**
Tegument protein; Virion host shutoff	**UL41; VHS**
VP26	**Capsid protein**
UL37	**Capsid assembly**
UL49A	**Envelope protein**

Figure (5)

(Sandra K. Weller ,Donald M. Coen,2012)

Transmission:

HSV-1(Oral Herpes) is mainly transmitted by oral-to-oral contact to cause oral herpes infection, via contact with the HSV-1 virus in sores, saliva, and surfaces in or around the mouth. However, HSV-1 can also be transmitted to the genital area through oral-genital contact to cause genital herpes.



HSV-1 can be transmitted from oral or skin surfaces that appear normal and when there are no symptoms present. However, the greatest risk of transmission is when there are active sores.

Individuals who already have HSV-1 oral herpes infection are unlikely to be subsequently infected with HSV-1 in the genital area.

In rare circumstances, HSV-1 infection can be transmitted from a mother with genital HSV-1 infection to her infant during delivery.

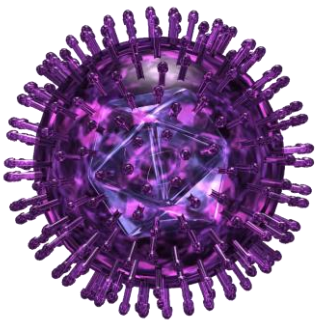
HSV-2 (Genital Herpes) infections often have no symptoms, or mild symptoms that go unrecognized. Most infected people are unaware that they have the infection. Typically, about 10-20% of people with HSV-2 infection report a prior diagnosis of genital herpes.

When symptoms do occur, genital herpes is characterized by one or more genital or anal blisters or open sores called ulcers. In addition to genital ulcers, symptoms of new genital herpes infections often include fever, body aches, and swollen lymph nodes.

After an initial genital herpes infection with HSV-2, recurrent symptoms are common but often less severe than the first outbreak. The frequency of outbreaks tends to decrease over time. People infected with HSV-2 may experience sensations of mild tingling or shooting pain in the legs, hips, and buttocks before the occurrence of genital ulcers.(2)

Penetration:

Attachment For HSV cell surface heparin sulphateis major binding factor.



Removal of HS does not remove attachment completely.

Most herpes viruses use more than one attachment pathway

Penetration Mediated by viral surface proteins –fusion of viral envelope with cell plasma membrane.

gB, gD and gH are all involved in fusion.

Transport Release of viral DNA into the nucleus is mediated by an unidentified viral function. (5)

Animation of penetration. (6)

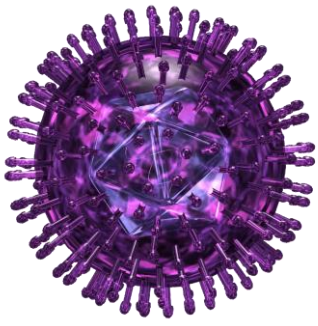
Replication cycle:

Penetration , The nucleocapsid enters the cell by direct membrane fusion plasma membrane .

In the lytic cycle, HSV infects epithelial cells located in the mucosa, replicates, and causes epithelial cell death . HSV-1 most frequently invades oral and ocular epithelial cells while HSV-2 infects the genital areas, but both strains have the ability to cause infection in either area of the body. (4)

Viral DNA into the nucleus. HSV replicates by three rounds of transcription that yield: (immediate early) proteins that mainly regulate viral replication; (early) proteins that synthesize and package DNA; and (late) proteins, most of which are virion proteins.

Of the 84 known polypeptides, at least 47 are not needed for viral replication in cultured 3 cells .



These 47 genes are not completely dispensable.

(Richard et al ,2001)

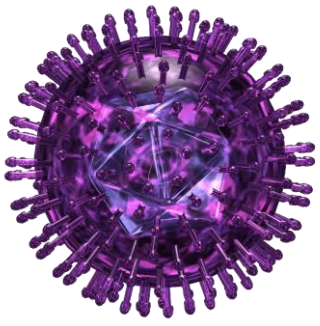
Central nervous system HSV replication in the brain causes encephalitis This is a life-threatening disease with a high mortality that causes permanent neurological damage in those who survive primary infection or secondary infection, and it is unclear how the virus enters the central nervous system.

Fortunately, the condition is rare (with an incidence of approximately 1 in 200 000 in the USA) and, if diagnosed at an early stage, responds to treatment with antiviral agents; these have significantly reduced the associated mortality and morbidity There is also epidemiological evidence that the presence of HSV-1 DNA in the brain might be associated with Alzheimer's disease, although no molecular mechanism for such a link has been proposed Congenital and neonatal infection Generalised HSV infection of the neonate has a very high mortality .

Infection is often acquired during passage through the birth canal but can also be acquired in utero. Caesarian section has been used in mothers with genital ulcers in an attempt to minimise the risks of peripartum transmission.

a) Herpes simplex virus (HSV) is shown undergoing the lytic cycle (entry, uncoating, viral transcription and DNA replication in the nucleus, particle assembly, exit from the cell) in epithelial cells of the skin to cause a primary infection.

(b) Some virus enters the sensory neuron terminals and travels retrogradely to the nucleus where it establishes latency.



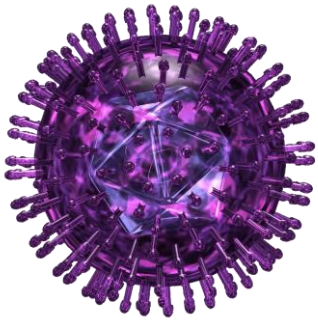
(c) Periodic reactivation results in anterograde transport of viral particles, shedding from the neuron, and re-infection of epithelial cells, which leads to asymptomatic shedding or recurrent lesions .

expression is dependent, to varying degrees, on prior synthesis of viral DNA. The products of the L genes are mostly structural components of the virion Viral protein synthesis occurs in the cytoplasm but the nucleocapsids are assembled within the nucleus. These nucleocapsidsrecognise the nascent viral genomes, which are cleaved into monomers as they are packaged. The completed nucleocapsids exit the nucleus by budding through the nuclear membrane.

The virus then exits the cell by traversing several membrane-bound organelles, where it acquires its mature envelope and glycoproteins Eventual cell lysis is the inevitable outcome of lytic infection with HSV- in tissue culture cells.

(Robin . 2003)

Animation of replication cycle: (7)



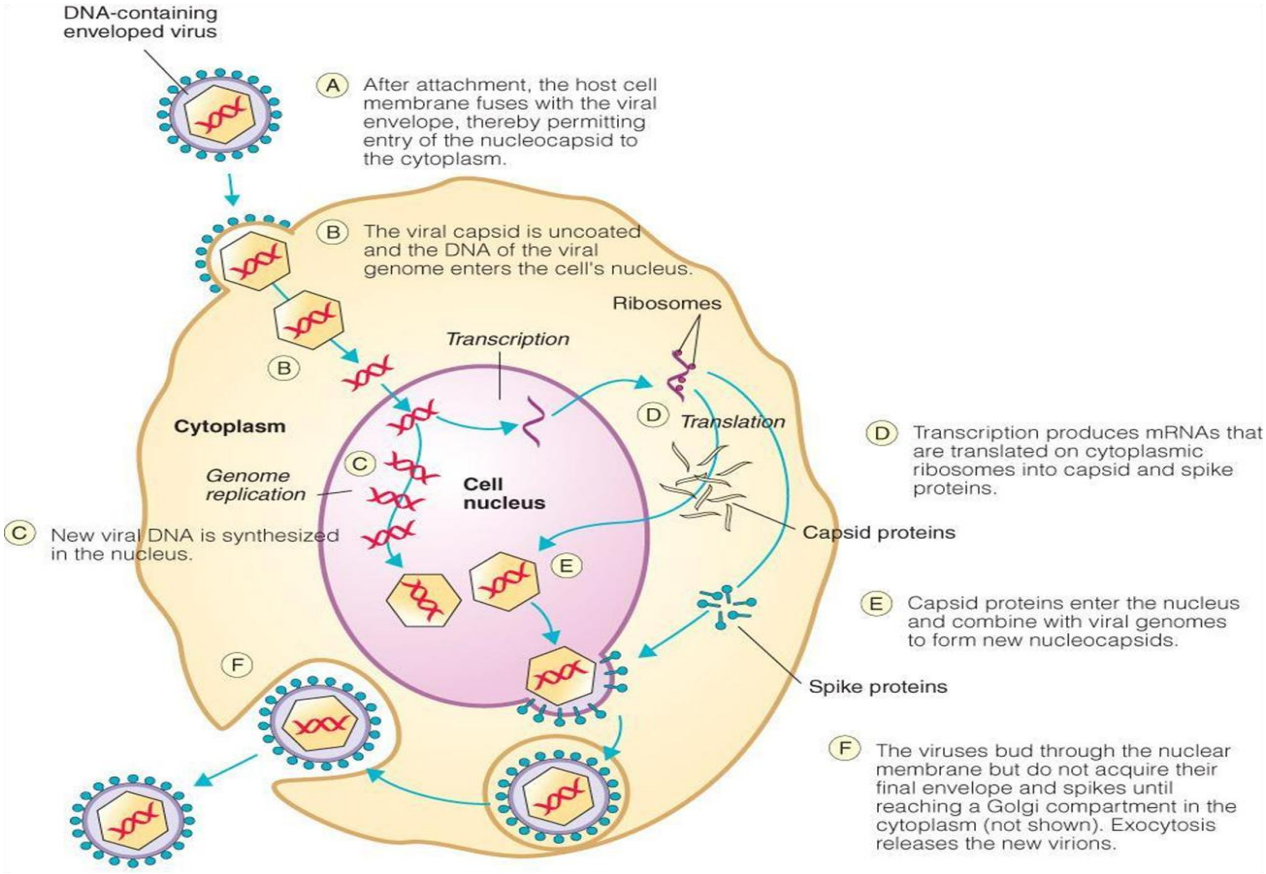
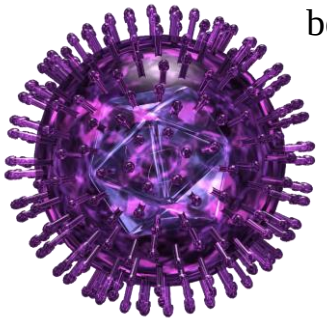


Figure (6)

Assembly and releases:

The proteins of the capsids are synthesized in the cytoplasm and aretranslocated from the cytoplasm to the nucleus where the capsids are assembled by an autocatalytic process.

morphogenesis and then confirmed by electronic microscopy According to this model, viral capsids in the nucleus bud at the internal nuclear membrane. Pre-enveloped viruses are then localized between the inner and the outer nuclear membrane. It was demonstrated that nuclear actin filaments are used to mobilize HSV-1viral capsids. The primary envelope acquired during budding through the innernuclear membrane is then lost because of the fusion with the external nuclear membrane. This leads to the release of free nude capsids into the cellular cytoplasm.



Capsids then transit in the cytoplasm to acquire, on one hand, tegument proteins and, on the other hand, envelope glycoproteins by budding in Golgi apparatus vesicles. Mature virions are then released at the surface of the cell by exocytosis.

(Sandra K. Weller ,Donald M. Coen,2012)

Signs and Symptoms:

Many people who get the virus that causes herpes never see or feel anything since after the first infection, the virus goes to sleep (becomes dormant) in the nerve tissues . Sometimes, the virus later wakes up (reactivates), causing cold sores. (1)

Oral Herpes Symptoms:

There are three stages to oral herpes after being infected:

a) Primary infection:

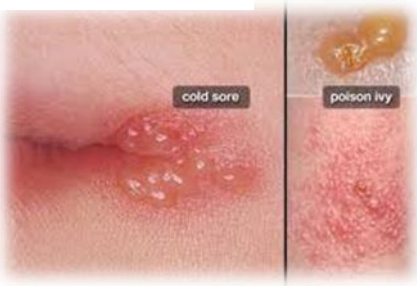
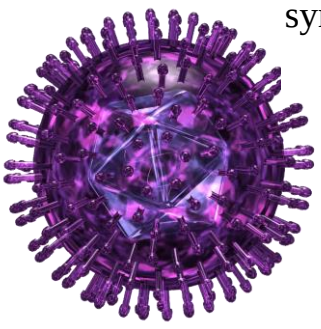


Figure (7)

The virus enters your skin or mucous membrane and reproduces. During this stage, oral sores and other symptoms, such as fever, may develop. However, the virus may not cause any sores and symptoms. You may not even know that you have it. This is called asymptomatic infection. Asymptomatic infections occur twice as often as the disease with symptoms.



b) Latency:

From the infected site, the virus moves to a mass of nervous tissue in spine called the dorsal root ganglion. There, the virus reproduces again and becomes inactive.

c) Recurrence:

When you experience certain emotional or physical stresses, the virus may reactivate and cause new sores and symptoms. One such stress may be a viral illness such as the common cold, hence the frequently used name of cold sores.(8)

Warning symptoms of itching, burning, increased sensitivity, or tingling sensation may occur about 2 days before lesions appear.

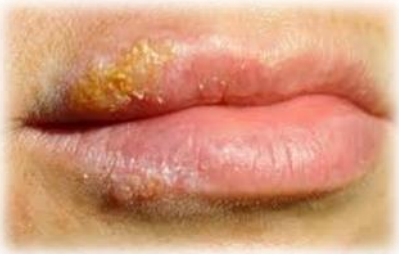
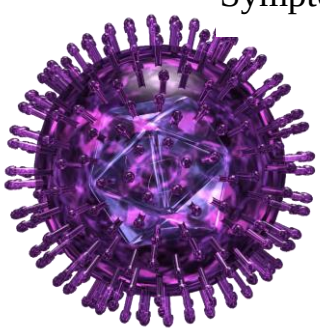


Figure (8)

- Skin lesions or rash around the lips, mouth, and gums
- Small blisters (vesicles) filled with clear yellowish fluid.
- Blisters on a raised, red, painful skin area
- Blisters that form, break, and ooze
- Yellow crusts that slough to reveal pink, healing skin
- Several smaller blisters that merge to form a larger blister
- Mild fever (may occur) (9)

Symptoms of Genital Herpes:

Symptoms may not appear until months or sometimes years after exposed to the virus.



If symptoms was for the first infected, they usually appear four to seven days after exposed to the virus. The symptoms are usually more severe first time around than in cases of recurrent infections.

a) Primary infection:

The symptoms of genital herpes for the first time include:

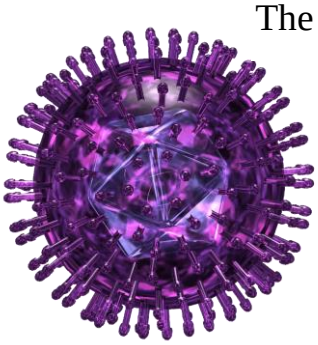
- small blisters that burst to leave red, open sores around genitals, rectum (back passage), thighs and buttocks
- blisters and ulcers on the cervix (lower part of the womb) in women
- vaginal discharge in women
- pain when you pass urine
- a general feeling of being unwell, with aches, pains and flu-like symptoms

These symptoms may last up to 20 days. However, the sores will eventually scab and heal without scarring.

Figure (9)

b) Recurrent infections:

Although the initial symptoms of genital herpes clear up, the virus remains dormant (inactive) in a nearby nerve. The virus may be reactivated from time to time,



travelling back down the nerve to skin and causing recurrent outbreaks.

Symptoms of a recurrent outbreak may include:

- a tingling, burning or itching sensation around genitals, and sometimes down to leg, before blisters appear
- painful red blisters that soon burst to leave sores around genitals, rectum (back passage), thighs and buttocks
- blisters and ulcers on the cervix (lower part of the womb) in women.

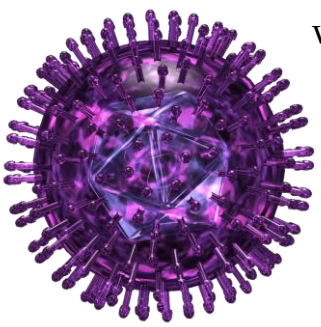
Recurrent outbreaks are usually shorter and less severe. This is because the body has produced protective antibodies (proteins that fight infection) in reaction to the previous infection. Your body now recognises the virus and mounts a response that is able to fight HSV more effectively.

Over time, any recurrent genital herpes infections become less frequent and less severe. (10)

Diagnosis and Cytopathic effect:

1. Laboratory tests:

Traditionally, tests involve taking a swab from an active lesion, growing the virus in the laboratory, and using colour-coded antibodies to pinpoint whether HSV-1 or HSV-2 is the culprit.



2. Use an electron microscope, to look for viral particles in fluid collected from the blisters and it considered faster but yields less information.

3. Using a highly accurate DNA test that can rapidly pick up the virus in a sample, and at the same time tell whether it is HSV-1 or HSV-2. And it considered more recently and many laboratories have moved to us this method.

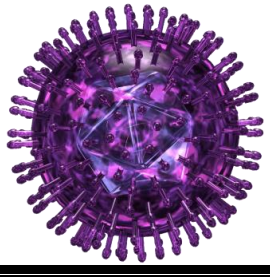
4. Doctors also sometimes take a blood sample, particularly in people with a history of possible herpes infection but no active lesions, to look for herpes antibodies. (3)

Figure (10)

Figure (11)

Figure (12)

Figure (13)



Control viruses:

- Antiviral (Acyclovir / Famciclovir / Valacyclovir) (11)
- Supportive , education, psychological support, analgesics, keep area clean and dry.
- No vaccine is available .(12)

Figure (14)

Figure (15)

Figure (16)

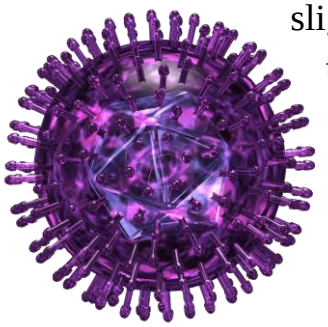
Currently, the only commercially available treatperments for recurrent genital herpes are the antiviral agents aciclovir, famciclovir and valaciclovir.

These agents act to prevent viral replication, and thereby limit viral spread to other cells, They may be used for the primary outbreak, on an episodic basis for recurrences, or chronically as suppressive therapy.

In most cases the management is mainly supportive with particular emphasis on keeping the child well hydrated.

The oral lesions are painful and topical acyclovir makes little difference. In any case most children are very distressed by attempts to touch the lesions.

Oral antivirals are not routinely recommended,3,4 as the risk of side effects is felt to outweigh the benefit (although there is evidence that they slightly reduce duration of the episode if given in the first three days).

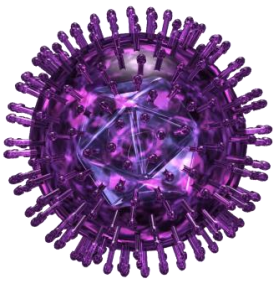


They are sometimes used for children admitted to hospital with dehydration secondary to gingivostomatitis.

(Lowth et al, 2014)

Recent discoveries:

The initial study population comprised 351,865 individuals, of whom 42,954 zoster cases with incident ischemic stroke and 24,237 zoster cases with acute MI fulfilled the eligibility criteria and were included in the primary analysis (Figure 17). Characteristics of these individuals are presented in Table 18. The median age at zoster diagnosis was 80 y (interquartile range [IQR] 74–86 y), and the median observation period was 5 y (IQR 4–5 y). The majority of participants were female (71% of zoster cases with stroke, 64% of zoster cases with MI); 89% of participants were white (88% of strokes, 90% of MIs), 5% were black, and the remaining 6% were Asian (2%), Hispanic (2%), or of other/unknown ethnicity (2%). In all, 16% of zoster cases had HZO; the remaining 84% had zoster of an unspecified site. Also, 34% of cases were of low income, and 90% had evidence of preexisting CVD before zoster diagnosis.



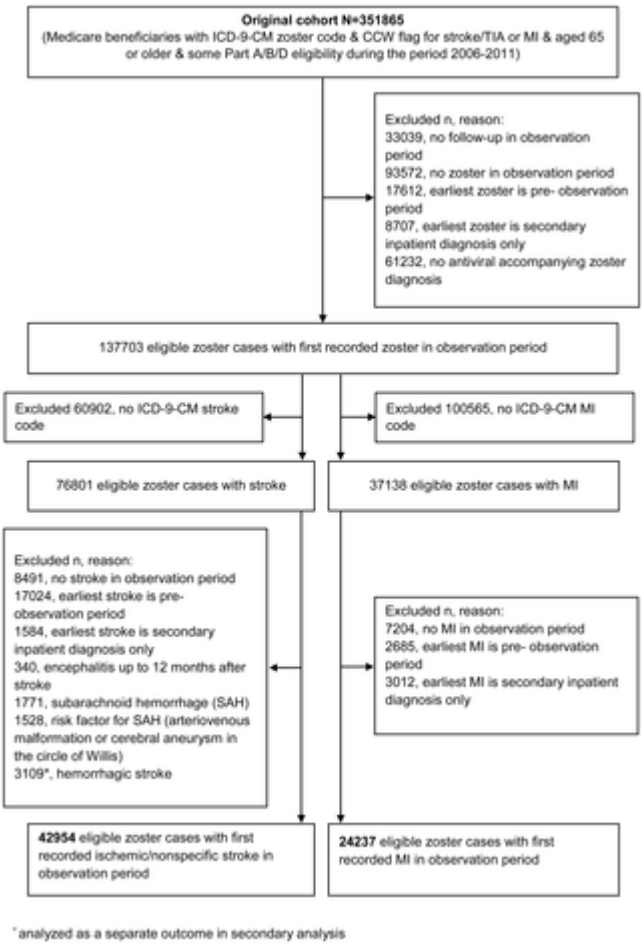


Figure (17) Identification of study participants

Characteristic	Zoster Cases with Ischemic Stroke (*n* = 42,954)	Zoster Cases with MI (*n* = 24,237)
HZO	6,971 (16.2%)	3,946 (16.3%)
Age at zoster diagnosis (years)	80.4 (74.4–85.9)	79.7 (73.5–85.5)
65–69	4,330 (10.1%)	2,854 (11.8%)
70–79	16,354 (38.1%)	9,602 (39.6%)
80–89	17,568 (40.9%)	9,286 (38.3%)
≥90	4,702 (10.9%)	2,495 (10.3%)
Age at HZO diagnosis (years)	81.1 (75.0–86.4)	80.3 (74.2–86.2)
Gender		
Male	12,672 (29.5%)	8,640 (35.6%)
Female	30,282 (70.5%)	15,597 (64.4%)
Ethnicity		
White	37,943 (88.3%)	21,693 (89.5%)
Black	2,319 (5.4%)	1,151 (4.8%)
Asian	970 (2.3%)	461 (1.9%)
Hispanic	1,033 (2.4%)	555 (2.3%)
Other/unknown	689 (1.6%)	377 (1.5%)
Low income[a]	14,742 (34.3%)	8,265 (34.1%)
Number of prescriptions in 12 mo before vascular event	48 (28–77)	51 (29–81)
CVD before zoster[b]	38,496 (89.6%)	21,969 (90.6%)
Risk factor for CVD before zoster[c]	42,216 (98.3%)	23,916 (98.7%)
Total observation (years)	5.0 (4.0–5.0)	5.0 (3.8–5.0)
Zoster vaccination status		
Vaccinated before zoster	1,213 (2.8%)	567 (2.3%)
Vaccinated after zoster[d]	2,759 (6.4%)	1,351 (5.6%)
Unvaccinated	38,982 (90.8%)	22,319 (92.1%)
Died or follow-up ended ≤90 d after vascular event	4,304 (10.0%)	3,986 (16.4%)

Data are given as *n* (percent) or median (IQR).
[a]State buy-in at any time during enrollment.
[b]MI, stroke, transient ischemic attack, ischemic heart disease, heart failure, or atrial fibrillation.
[c]Hypertension, hyperlipidemia, diabetes, chronic kidney disease, or chronic obstructive pulmonary disease.
[d]Includes 27 stroke cases and 19 MI cases who received vaccine on day of zoster diagnosis.

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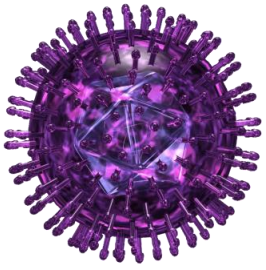
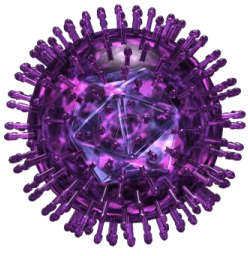


Table (18) Participant characteristics

A small minority of cases received the zoster vaccine before developing zoster (3% of cases with stroke, 2% of cases with MI), 6% received the vaccine after zoster diagnosis, and 91% were unvaccinated throughout the observation period. Characteristics of individuals included in the analyses stratified by zoster vaccination status are given in S1 Table. Vaccinated and unvaccinated individuals had similar median age, gender, and preexisting CVD risk profiles, although unvaccinated individuals were more than twice as likely to be of low income and received more prescriptions in the year leading up to their vascular event compared to vaccinated individuals. Ethnicity data among vaccinated individuals could not be reported because some numbers were small enough to be restricted by the CMS small-sized-cell privacy policy.

The rate of ischemic stroke was significantly increased up to 3 mo after zoster diagnosis (any site) compared to the baseline rate: the most marked increase, 2.4-fold, was observed within the first week (IR 2.37, 95% CI 2.17–2.59), reducing to 1.6-fold in weeks 2–4 (IR 1.55, 95% CI 1.46–1.66), 1.2-fold in weeks 5–12 (IR 1.17, 95% CI 1.11–1.22), and resolving over the subsequent 3 mo (weeks 13–26: IR 1.03, 95% CI 0.99–1.07; weeks 27–52: IR 1.00, 95% CI 0.96–1.03). A similar though less marked association was observed for MI in the 3 mo after zoster diagnosis, with a 68% increased MI rate in the first week (IR 1.68, 95% CI 1.47–1.92) compared to baseline and a similar pattern of resolution as for stroke (weeks 2–4: IR 1.25, 95% CI 1.14–1.37; weeks 5–12: IR 1.07, 95% CI 1.00–1.14; weeks 13–26: IR 1.02, 95% CI 0.96–1.07; weeks 27–52: IR 1.02, 95% CI 0.98–1.07) (Table 19).



Risk Period	Number of Ischemic Stroke Cases (n = 42,954)	Ischemic Stroke IR* (95% CI)	Number of MI Cases (n = 24,237)	MI IR* (95% CI)
Baseline	32,179	1	18,071	1
Risk period after zoster				
1 wk	499	2.37 (2.17–2.59)†	213	1.68 (1.47–1.92)†
2–4 wk	967	1.55 (1.46–1.66)†	470	1.25 (1.14–1.37)†
5–12 wk	1,841	1.17 (1.11–1.22)†	1,019	1.07 (1.00–1.14)‡
13–26 wk	2,588	1.03 (0.99–1.07)	1,537	1.02 (0.96–1.07)
27–52 wk	3,981	1.00 (0.96–1.03)	2,459	1.02 (0.98–1.07)

*IRs age-adjusted in 2-y bands.
†p < 0.001.
‡p < 0.05.

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Table (19) Primary analysis: age-adjusted incidence ratios for ischemic stroke and myocardial infarction in risk periods after zoster diagnosis.

Analyses restricted to cases with HZO (*n* = 6,971 with ischemic stroke, 3,946 with MI) yielded associations comparable to those of the primary analysis (week 1 after HZO diagnosis: stroke IR 2.73, 95% CI 2.22–3.35; MI IR 2.06, 95% CI 1.52–2.79) that resolved over the same time period (Table 20).

Risk Period	Number of Ischemic Stroke Cases (n = 6,971)	Ischemic Stroke IR* (95% CI)	Number of MI Cases (n = 3,946)	MI IR* (95% CI)
Baseline	5,125	1	2,891	1
Risk period after HZO				
1 wk	93	2.73 (2.22–3.35)†	43	2.06 (1.52–2.79)†
2–4 wk	177	1.77 (1.52–2.05)†	85	1.38 (1.11–1.72)‡
5–12 wk	326	1.29 (1.15–1.44)†	160	1.02 (0.87–1.20)
13–26 wk	428	1.06 (0.96–1.17)	282	1.15 (1.01–1.30)‡
27–52 wk	651	1.02 (0.94–1.11)	421	1.07 (0.97–1.19)

*IRs age-adjusted in 2-y bands.
†p < 0.005.
‡p < 0.05

doi:10.1371/journal.pmed.1001919.t003

Table (20) Age-adjusted incidence ratios for ischemic stroke and myocardial infarction in risk periods after herpes zoster ophthalmicus.

Stratifying by zoster vaccination status revealed no evidence for a reduced IR for ischemic stroke during the first 4 wk after zoster diagnosis among individuals who received the zoster vaccine (*n* = 843) (IR 1.14, 95% CI 0.75–1.74) compared to unvaccinated individuals (*n* = 40,724) (IR 1.78, 95% CI 1.68–1.88) (*p*-value for interaction = 0.28). The overall IR combining vaccinated and unvaccinated individuals for the same 4-wk post-zoster period was 1.76 (95% CI 1.67–1.86). There was no evidence that the IR for MI after zoster diagnosis varied according to zoster vaccination status (*p* = 0.44): the IR in weeks 1–4 after zoster diagnosis was 1.36 (95% CI 0.78–2.39) in vaccinated individuals (*n* = 400) and

1.37 (95% CI 1.26–1.48) in unvaccinated individuals (*n* = 23,089), similar to the combined IR of 1.37 (95% CI 1.26–1.48) (Table 21).

Outcome	Risk Period	Vaccinated[a]		Unvaccinated	
		Number of Cases	IR[b] (95% CI)	Number of Cases	IR[b] (95% CI)
Ischemic stroke		843		40,724	
	Baseline	602	1	30,412	1
	Risk period after zoster				
	1–4 wk	23	1.14 (0.75–1.74)	1,436	1.78 (1.68–1.88)
	5–12 wk	50	1.30 (0.97–1.74)	1,778	1.17 (1.11–1.23)
	13–26 wk	64	1.12 (0.86–1.46)	2,467	1.03 (0.99–1.07)
	27–52 wk	81	0.97 (0.76–1.24)	3,756	1.00 (0.97–1.04)
MI		400		23,089	
	Baseline	272	1	17,180	1
	Risk period after zoster				
	1–4 wk	13	1.36 (0.78–2.39)	868	1.37 (1.28–1.46)
	5–12 wk	18	1.04 (0.64–1.69)	992	1.07 (1.01–1.15)
	13–26 wk	37	1.49 (1.05–2.13)	1,466	1.01 (0.96–1.07)
	27–52 wk	46	1.21 (0.87–1.69)	2,329	1.02 (0.98–1.07)

Note that the analyses of MI excluded 167 vaccinated individuals whose MI or zoster occurred before the adjusted start date and 581 unvaccinated individuals whose MI occurred after the adjusted end date; the analyses of stroke excluded 370 vaccinated individuals whose stroke or zoster occurred before the adjusted start date and 1,017 unvaccinated individuals whose stroke occurred after the adjusted end date.

[a]p-Values for interaction: stroke, $p = 0.28$; MI, $p = 0.44$.

[b]IRs age-adjusted in 2-y bands.

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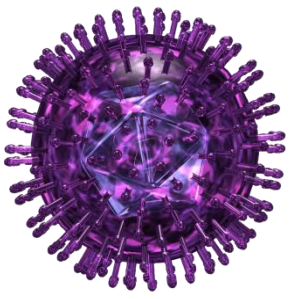
Table (21) Age-adjusted incidence ratios for vascular events in risk periods after zoster diagnosis, stratified by vaccination status.

The secondary analysis of hemorrhagic stroke (*n* = 3,109 cases) indicated a similar pattern of increase and resolution of risk as for ischemic/nonspecific stroke, though less pronounced and with reduced precision because of the relatively few cases. The largest increase in hemorrhagic stroke rate, 1.6-fold, was observed in weeks 2–4 post-zoster (IR 1.61, 95% CI 1.29–2.02), reducing to 1.3-fold in weeks 5–12 (IR 1.30, 95% CI 1.10–1.53) and resolving thereafter.

Using the extension to the standard SCCS method to allow for nonrandom censoring of observation gave results virtually identical to those obtained in the primary analysis (S2 Table). Further sensitivity analyses excluding potentially fatal cases also gave similar findings (S3 Table).

(Caroline Minassian et al, 2015)



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