

# Public Awareness and Knowledge of Herpes Labialis

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Between 20% and 40% of the population is estimated to suffer from episodes of recurrent herpes labialis, although few reports in the literature have addressed the public awareness of this infection in the general population. The aims of this study were to determine the existing level of awareness and knowledge of this disease and to assess the source of this knowledge, the ability of the public to recognize the characteristics of the disease and the behavior of patients with clinical cases of disease manifestation. To this end, 2,000 individuals (961 male and 1,039 female) of 14 years of age and older were surveyed using the ECOcapi system [Eurisko Consumer Omnibus—CAPI (computer-assisted personal interviewing) version]. Eighty-nine percent of those surveyed had some knowledge of herpes labialis; 92% were able to refer to at least one symptom of herpes labialis, 91% were able to identify correctly his infection from pictures, and 45% had experienced personally at least one episode of herpes labialis infection. The majority of the individuals suffering from herpes labialis self-medicated using a topical therapy. Women were found to be affected more commonly by herpes labialis than men [OR 1.42 (1.18–1.70)], and women were also more likely to recognize the disease [OR 1.65 (1.30–2.08)] and to seek medical advice for the condition [OR 1.38 (1.12–1.70)]. In conclusion, herpes labialis is a common and well-known condition, and it is often self-diagnosed correctly, as the prodromal phase and the use of self-medication are very common. **J. Med. Virol.** 9999:1–6, 2011. © 2011 Wiley-Liss, Inc.

**KEY WORDS:** herpes simplex virus; herpes labialis; public awareness; public health; epidemiology

## INTRODUCTION

Herpes simplex virus (HSV) infection is responsible for a wide array of human diseases that range from

mild, localized HSV infection in the general population to severe life-threatening infections in immunocompromized individuals. HSV-type 1 (HSV-1) infection is usually acquired during childhood and adolescence, and symptomatic infections are characterized by oral or facial lesions [Whitley et al., 2007]. Although HSV-1 is transmitted most often by non-sexual contact, data from certain developed countries indicate that an increasing proportion of first-episode genital herpes infections are caused by HSV-1, and this is the major pattern of infection in many areas [Smith and Robinson, 2002]. The seroprevalence of HSV-1 varies considerably, but it has been shown to increase with age, as 88% of individuals are seropositive at the age of 40 years and older [Wutzler et al., 2000].

Recurrent infections with herpes labialis, also known as "cold sores" or "fever blisters," are the most common manifestation of oral HSV-1 infection. Between 20% and 40% of the general population are estimated to suffer from herpes labialis [Higgins et al., 1993]. Given the high prevalence of HSV-1 infection, the susceptibility to HSV recurrence accounts for only a minor fraction of infected individuals. Additional factors that influence infection include the expression of genetic markers, epidermal cell susceptibility, the relative potency of different HSV strains and differences in the type and/or strength of antiviral immunity and interferon response [Kohl, 1992; Spruance et al., 1995; Casrouge et al., 2006; Seppanen et al., 2006; Kittan et al., 2007; Whitley et al., 2007; Paladino and Mossman, 2009; Pica et al., 2010].

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The effect of herpes labialis infection varies considerably from patient-to-patient; in some, infection is infrequent and considered a minor nuisance, but in others, the infection can become a frequent occurrence which is associated with physical signs and symptoms as well considerable social stigmatization due to its central facial location [Volpi and Stanberry, 2007]. Episodic or prophylactic treatment with antiviral therapy is the current standard of care for herpes labialis [Gilbert et al., 2007].

Herpes labialis is a clinical condition that has been known for centuries. The prevalence of this infection throughout history is documented in the following line delivered by Mercutio in Act I, scene IV of *Romeo and Juliet*: "O'er ladies' lips, who straight on kisses dream, Which oft the angry Mab with blisters plagues" [Shakespeare, 1599]. However, few recent reports in the literature have addressed the public awareness of this infection [Axel and Liedholm, 1990; Lamey and Biagioni, 1996; Gallais et al., 2000; Lowhagen et al., 2002]. Furthermore, there have been few recent studies that have focused on the prevalence of symptomatic herpes labialis in selected countries [Kleinman et al., 1994; Cowan et al., 1996; Lamey and Biagioni, 1996; Gallais et al., 2000].

Due to the absence of objective data in the literature concerning the public knowledge of herpes labialis, this large investigation examined the existing level of public awareness and knowledge of this infection in Italy and assessed the source of this knowledge, the ability to recognize accurately the infection and the behavior of patients with clinical manifestations.

## METHODS

The Herpes Labialis Awareness Survey was conducted between June 7 and June 17, 2005 in Italy. A questionnaire was designed which was administered by GfK Eurisko (<http://www.gfk.com/gfk-eurisko/>), a firm that provides information services and analyses in several fields including that of health care.

The survey was conducted using the ECOcapi system [Eurisko Consumer Omnibus, CAPI (computer-assisted personal interviewing) version]. This system consisted of face-to-face interviews performed with the aid of a laptop computer to show the questionnaire as well as the pictures and video applications.

The questionnaire consisted of seven multiple-choice questions (one closed-ended and six open-ended) that addressed the following three broad themes: the knowledge, symptoms and treatment of herpes labialis (Fig. 1). The term "herpes labialis" and the local term "febbre del labbro" (cold sores) were used in the interviews. The answers provided by the interviewees were entered immediately into the survey by the interviewer for quality control and expedient data processing. The data were processed by the Eurisko Centro Elaborazione Dati and were expressed as percentages of the total sample.

A total of 2,000 individuals of 14 years of age and older, who were selected at random from different regions of Italy, were enrolled in the study and characterized by age, gender, profession, geographic distribution, and highest level of education. The participants were informed of the aim of the survey, and each participant provided informed consent for the interview. According to Italian regulations, research involving the use of educational tests, survey procedures, interview procedures or the observation of public behavior is exempt from the requirement for approval by an ethical committee.

## RESULTS

Of the 2,000 individuals enrolled in the study, 961 were male and 1,039 female, and all the individuals were white Caucasian Italians. The sample population studied was representative of the Italian population in terms of age, gender, geographic distribution, educational level, and occupation. The demographic characteristics of the individuals surveyed are shown in Table I.

Eighty-nine percent of the individuals surveyed (1,781 out of 2,000 individuals) were found to possess some knowledge of herpes labialis. However, the degree of the knowledge possessed was not consistent among individuals of all ages; individuals under 17 years of age and over 64 years of age were found to have a lower degree of knowledge (84% and 86%, respectively), and the degree of knowledge was highest (92%) in adults between 35 and 45 years of age (data not shown).

Seventy-two percent of those who had knowledge of herpes labialis had acquired it from parents/relatives or friends/acquaintances. Only 21% and 7% of these individuals received this information from a physician or pharmacist, respectively, and this was more common in older people (29% and 10%, respectively, for individuals over 45 years of age) than younger people (8% and 1%, respectively, for individuals aged between 14 and 17 years of age).

Ninety-two percent of the individuals who had some knowledge of herpes labialis were able to name at least one symptom/sign of the disease ("swelling" followed by the occurrence of "blisters" was the most frequently cited symptom/sign), and 91% of these individuals were able to correctly identify the infection from pictures shown on a computer screen.

Forty percent of the total sample population and 45% of those who had knowledge of herpes labialis had personally experienced this infection at least once. Of these, 25% reported to have had a single herpes labialis episode, 33% reported to have had two or three episodes, and 42% reported to have had more than three episodes.

Of the individuals who had experienced at least one episode of herpes labialis, the first signs or symptoms identified were swelling (47%) and itching (51%), and this indicated a moderate level of public knowledge on

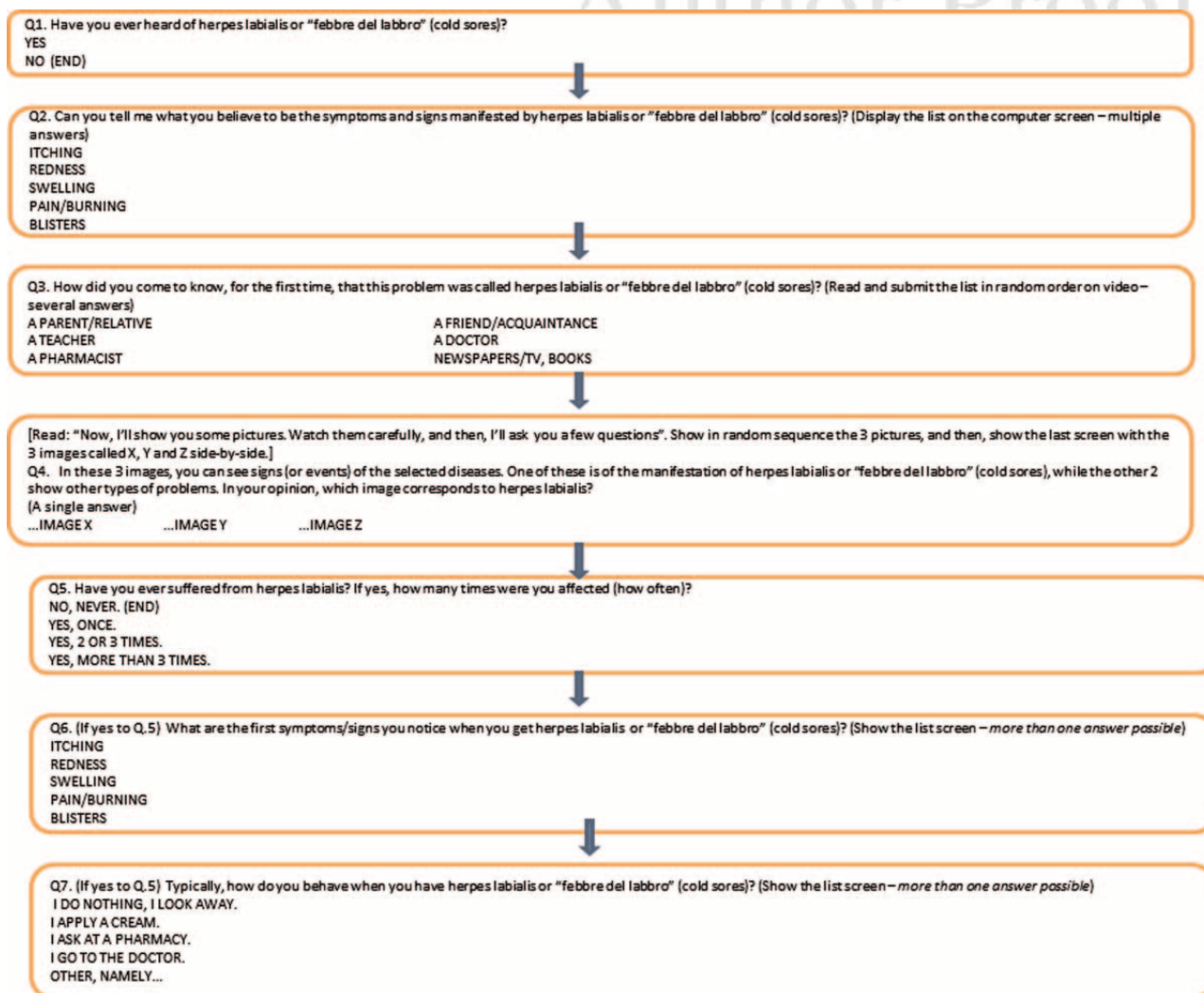


Fig. 1. This flow chart summarizes the sequences of questions and possible answers that determined the respondents' knowledge of herpes labialis infection, the spectrum of symptoms/signs experienced, the frequency of herpes labialis episodes, and the different behaviors and types of treatments received.

the prodromes of herpes labialis. An illustration of the percentages of people surveyed from the general population who had knowledge of, recognized or suffered from herpes labialis infections is shown in Figure 2.

Eighty-one percent of those who had experienced at least one episode of herpes labialis (654 out of 807 individuals) reported at least one behavioral response, and the remaining individuals did not. Among those who responded to their infection, 496 (61.4%) self-medicated using a topical cream, 78 (9.7%) sought medical advice, 91 (12.2%) asked for the advice of a pharmacist and the remainder used various natural products. Interestingly, the frequency of using a cream was the same for those who sought medical advice and those who did not (65.9% and 59.7%, respectively).

Finally, herpes labialis infection was more frequently reported by females than males [44% vs. 36%,

respectively; OR 1.42 (1.18–1.70)], and women were also more likely than men to recognize the disease [91% vs. 86%, respectively; OR 1.65 (1.30–2.08)], to recognize the disease from pictures (85% vs. 77%) and to implement at least one behavior in response to infection with herpes labialis [83% vs. 78.5%, respectively; OR 1.38 (1.12–1.70)].

## DISCUSSION

The results of the present study demonstrate that herpes labialis is a well-known disease. The respondents in the survey consistently demonstrated a significant level of knowledge about the characteristic signs and symptoms of herpes labialis (92% of these individuals cited the presence of swelling and typical vesicles) and were able to recognize and differentiate herpes labialis infection from other pathological



TABLE I. The Distribution of the Sample Population According to Age, Gender, Geographic Area, Educational Level and Occupation

	Males, No. (%)	Females, No. (%)
<b>Age</b>		
14–24	142 (14.8)	136 (13.1)
25–34	180 (18.7)	176 (16.9)
35–44	178 (18.6)	176 (17.0)
45–54	152 (15.8)	155 (14.9)
55–64	132 (13.8)	142 (13.7)
>64	177 (18.4)	254 (24.4)
Total	961 (100)	1,039 (100)
<b>Geographic area</b>		
North West	282 (29.4)	251 (24.2)
North East	161 (16.7)	217 (20.9)
Centre	181 (18.8)	209 (20.1)
South and Islands	337 (35.1)	362 (34.8)
<b>Years of education</b>		
Primary	216 (22.4)	343 (33)
Secondary	398 (41.4)	380 (36.6)
High school	276 (28.7)	250 (24)
University Degree	72 (7.5)	66 (6.4)
<b>Occupation</b>		
Professional position	579 (60.2)	321 (30.9)
Entrepreneur/freelance professions	176 (18.3)	74 (7.1)
Officer/employee/teacher	183 (19)	163 (15.7)
Worker	221 (23)	84 (8.1)
Position not professional	382 (39.8)	718 (69.1)
Housewife		345 (33.2)
Student	85 (8.8)	88 (8.5)
Retired	217 (22.6)	213 (20.5)
Unemployed	80 (8.4)	71 (6–9)

conditions such as angular cheilitis or perioral acne. As expected, the exclusion of the youngest and oldest individuals from the sample population analyzed resulted in an increase in the percentage of subjects who knew of and could correctly recognize herpes labialis infection. These results obtained for Italian people are in alignment with those reported from studies in

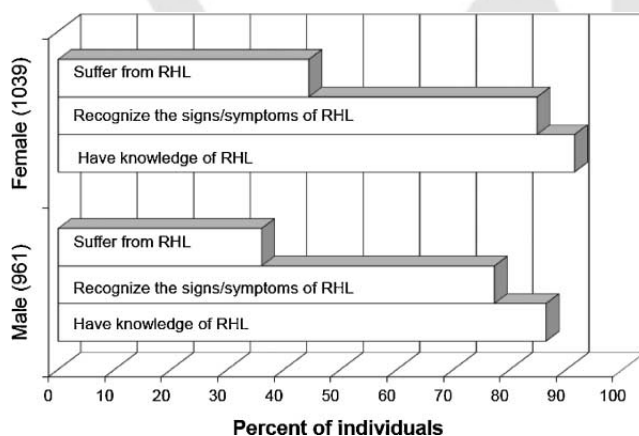


Fig. 2. The relative percentages of people in the studied sample population who demonstrated knowledge of, suffered from or recognized recurrent herpes labialis (RHL) infections.

other European countries [Axel and Liedholm, 1990; Kleinman et al., 1994; Cowan et al., 1996; Lamey and Biagioni, 1996; Gallais et al., 2000; Lowhagen et al., 2002].

It is likely that both the high prevalence of HSV-1 infection in the general population and the typical clinical manifestation of herpes labialis enable individuals to know/recognize this infection following the first episode. In the majority of cases, the clinical outbreaks of herpes labialis are commonly preceded by a series of local prodromes, such as pain, tingling, burning, or itching, which are promptly noted and memorized subsequently by the subjects.

Thus, the likelihood that herpes labialis would be confused with other clinical conditions, such as acne, pimples, warts, insect bites, or impetigo, seems rather remote. However, a delayed diagnosis would be of little harm to the patient. In the present study, the possible risk of an over-diagnosis of herpes labialis was avoided by supplying the participants with informative descriptions (both in written text and pictures) on a computer screen during the face-to-face interviews, and this may have increased the validity of the correct diagnosis.

The second significant result of the present study was the finding that the majority of individuals obtained their knowledge of herpes labialis from parents/relatives and friends/acquaintances, and only a minority of the individuals obtained this information from a physician. Indeed, this is a characteristic feature of many ancient and widespread diseases in the world.

In the present study, 40% of the individuals surveyed had experienced at least one episode of herpes labialis. This percentage is very similar to that reported recently by a French study (39.9%) [Gallais et al., 2000], but is significantly greater than that found in Sweden (26.6%) [Lowhagen et al., 2002].

Large inter-country differences in the seroepidemiology of HSV-1 have been documented around the world [Nahmias et al., 1990]. In Europe, the risk for the acquisition of HSV-1 infection has been linked to socio-demographic status, and a north-south/east gradient has been demonstrated for this phenomenon [Pebody et al., 2004]. Furthermore, an inverse correlation between the age-standardized seroprevalence of HSV-1 and the national gross domestic product (correlation = 20.93) has been reported. A large proportion of adolescents remain susceptible to HSV-1 infection in northern Europe, which suggests that the age-dependent force (or risk) of infection for HSV-1 is greater in Southern and Eastern Europe than in Northern Europe. These differences in the epidemiology of HSV-1 have likely occurred only recently [Vyse et al., 2000] and may reflect changes in socioeconomic status and family size [Pebody et al., 2004].

A trend towards an increasing percentage of individuals who have experienced at least one episode of herpes labialis infection was found for those individuals in their middle ages of life (data not shown), which

is in line with previous observations [Higgins et al., 1993; Wutzler et al., 2000; Smith and Robinson, 2002]. This finding highlights the role of the horizontal spread of the virus among individuals. It has been shown that both primary and recurrent infections result in significant reservoirs of virus that have the potential for transmission to oral and genital sites during periods of intimate contact with other individuals. Symptomatic infections pose the greatest risk for transmission, but the risk of transmission persists during periods of asymptomatic virus shedding [Sacks et al., 2004; Volpi and Stanberry, 2007]. As discussed above, orogenital transmission is a major route for genital HSV-1 infection [Sacks et al., 2004], and for this reason, a greater awareness of the possible risks for the transmission of herpes labialis during an active episode should be promoted among people.

According to the results described above, herpes labialis infection is more common in females than in males. Similar gender differences for clinical disease as well as for estimations of seroprevalence have been reported by other studies [Axel and Liedholm, 1990; Nahmias et al., 1990; Kleinman et al., 1994; Cowan et al., 1996; Vyse et al., 2000; Lowhagen et al., 2002; Pebody et al., 2004].

Finally, the observation that the behavior of Italian and French persons in regards to herpes labialis infection are similar both in terms of the percentages of individuals who seek medical advice (9.7% and 7.5%, respectively) and those who use self-medication (61.4% and 62.9%, respectively) [Gallais et al., 2000].

On the basis of the present investigation and in line with published reports, it is concluded that herpes labialis is a very frequent infection with a well-known pathology. The clinical manifestations of this disease are usually self-diagnosed correctly by the patients even during the prodromal phase, which is very relevant to antiviral therapy because this treatment is recommended to be initiated in the prodromal phase [Gilbert et al., 2007].

According to the data presented above, physicians are not consulted frequently by individuals affected by herpes labialis, and the use of self-medication is very frequent among adults who are active professionally but is less frequent among older individuals. Furthermore, the tendency to seek medical advice increases only in cases with particularly severe clinical manifestations.

However, the burden of herpes labialis is often underestimated by physicians and regulatory authorities. As an example, in Italy, the use of antiviral drugs for the episodic and suppressive treatment of genital herpes is funded by the national health service; however, this treatment does not cover infections with herpes labialis. This policy is common in other parts of the world as well, and it places severe limitations on the wellbeing of patients [Volpi and Stanberry, 2007].

The ability of the people to self-administer appropriate treatments for herpes labialis infections appears

to be confirmed. It is therefore conceivable to hypothesize that an increased availability of over-the-counter systemic and topical antiviral drugs would aid in the correct self-medication of the general population in the absence of any significant risks to public health.

## REFERENCES

- Axel T, Liedholm R. 1990. Occurrence of recurrent herpes labialis in an adult Swedish population. *Acta Odontol Scand* 48:119–123.
- Casrouge A, Zhang SY, Eidenschenk C, Jouanguy E, Puel A, Yang K, Alcais A, Picard C, Mahfoufi N, Nicolas N, Lorenzo L, Plan-coulaine S, Sénéchal B, Geissmann F, Tabeta K, Hoebe K, Du X, Miller RL, Héron B, Mignot C, de Villemeur TB, Lebon P, Dulac O, Rozenberg F, Beutler B, Tardieu M, Abel L, Casanova JL. 2006. Herpes simplex encephalitis in human UNC-93B deficiency. *Science* 314:308–312.
- Cowan FM, Johnson AM, Ashley R, Corey L, Mindel A. 1996. Relationship between antibodies to herpes simplex virus (HSV) and symptoms of HSV infection. *J Infect Dis* 174:470–475.
- Gallais J, Boissault P, Morel F, Clerc P, Letrillard L, Hebbrecht G. 2000. Herpes labialis and genitalis in general medicine. *Ann Dermatol Venereol* 127:596–602.
- Gilbert S, Corey L, Cunningham A, Malkin JE, Stanberry L, Whitley R, Spruance S. 2007. An update on short-course intermittent and prevention therapies for herpes labialis. *Herpes* 14:13A–18A.
- Higgins CR, Schofield JK, Tatnall FM, Leigh IM. 1993. [Natural<sup>Q1</sup>](#) history, management and complications of herpes labialis. *J Med Virol* XX:22–26.
- Kittan NA, Bergua A, Haupt S, Donhauser N, Schuster P, Korn K, Harrer T, Schmidt B. 2007. Impaired plasmacytoid dendritic cell innate immune responses in patients with herpes virus-associated acute retinal necrosis. *J Immunol* 179:4219–4230.
- Kleinman DV, Swango PA, Pindborg JJ. 1994. Epidemiology of oral mucosal lesions in United States schoolchildren: 1986–1987. *Community Dent Oral Epidemiol* 22:243–253.
- Kohl S. 1992. The role of antibody in herpes simplex virus infection in humans. *Curr Top Microbiol Immunol* 179:75–88.
- Lamey PJ, Biagioni PA. 1996. Patient recognition of recrudescing herpes labialis: A clinical and virological assessment. *J Dent* 24:325–327.
- Lowhagen GB, Bonde E, Eriksson B, Nordin P, Tunbäck P, Krantz I. 2002. Self-reported herpes labialis in a Swedish population. *Scand J Infect Dis* 34:664–667.
- Nahmias AJ, Lee FK, Beckman-Nahmias S. 1990. Sero-epidemiological and sociological patterns of herpes simplex virus infection in the world. *Scand J Infect Dis* 69:19–36.
- Paladino P, Mossman KL. 2009. Mechanisms employed by herpes simplex virus 1 to inhibit the interferon response. *J Interferon Cytokine Res* 29:599–607.
- Pebody RG, Andrews N, Brown D, Gopal R, De Melker H, François G, Gatcheva N, Hellenbrand W, Jokinen S, Klavs I, Kojouharova M, Kortbeek T, Kriz B, Prosenic K, Roubalova K, Teocharov P, Thierfelder W, Valle M, Van Damme P, Vranckx R. 2004. The seroepidemiology of herpes simplex virus type 1 and 2 in Europe. *Sex Transm Infect* 80:185–191.
- Pica F, Volpi A, Gaziano R, Garaci E. 2010. Interferon-lambda in immunocompetent individuals with a history of recurrent herpes labialis. *Antivir Ther* 15:737–743.
- Sacks SL, Griffiths PD, Corey L, Cohen C, Cunningham A, Dusheiko GM, Self S, Spruance S, Stanberry LR, Wald A, Whitley RJ. 2004. HSV shedding. *Antiviral Res* 63:S19–S26.
- Seppanen M, Meri S, Notkola IL, Seppala JJ, Hiltunen-Back E, Sarvas H, Lappalainen M, Valimaa H, Palikhe A, Valtonen VV, Lokki ML. 2006. Subtly impaired humoral immunity predispose to frequently recurring genital herpes simplex virus type 2 infection and herpetic neuralgia. *J Infect Dis* 194:571–578.
- Shakespeare W. 1599. Mercutio talk. In “Romeo and Juliet”, Act I, scene IV.
- Smith JS, Robinson NJ. 2002. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: A global review. *J Infect Dis* 186:S3–S28.
- Spruance LS, Evans TG, McKeough MB. 1995. Th1/th2-like immunity and resistance to herpes simplex labialis. *Antiviral Res* 28:39–55.

- Volpi A, Stanberry L. 2007. Tailoring herpes labialis treatments. *Herpes* 14:55.
- Vyse AJ, Gay NJ, Slomka MJ, Gopal R, Gibbs T, Morgan-Capner P, Brown DW. 2000. The burden of infection with HSV-1 and HSV-2 in England and Wales: Implications for the changing epidemiology of genital herpes. *Sex Transm Infect* 76:183–187.
- Whitley R, Kimberlin DW, Prober CG. 2007. Pathogenesis and disease. In: Arvin A, Campadelli-Fiume G, Mocarski E, Moore PS, Roizman B, Whitley R, Yamanishi K, editors. *Human herpesviruses: Biology, therapy, and immunoprophylaxis*. Cambridge: Cambridge University Press, Chapter 32.
- Wutzler P, Doerr HW, Färber I, Eichhorn U, Helbig B, Sauerbrei A, Brandstädt A, Rabenau HF. 2000. Seroprevalence of herpes simplex virus type 1 and type 2 in selected German populations: Relevance for the incidence of genital herpes. *J Med Virol* 61:201–207.



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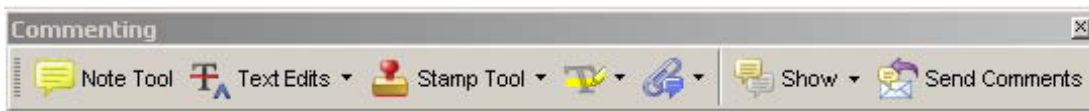
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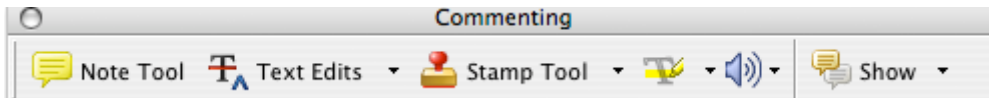
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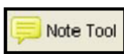
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