Schizophrenia Research 136 (2012) 128–136

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Infectious agents associated with schizophrenia: A meta-analysis

Isabel Arias [a], Antonio Sorlozano [b,*], Enrique Villegas [b], Juan de Dios Luna [c], Kathryn McKenney [d], Jorge Cervilla [d,e], Blanca Gutierrez [d], Jose Gutierrez [b,f]

[a] CAP El Clot, Institut Català de la Salut, Barcelona, Spain
[b] Department of Microbiology, School of Medicine, University of Granada, Spain
[c] Department of Statistics and Operation Research, University of Granada, Spain
[d] Department of Psychiatry, Institute of Neurosciences & CIBERSAM, University of Granada, Spain
[e] Mental Health Unit, San Cecilio University Hospital, Granada, Spain
[f] Service of Microbiology, Virgen de las Nieves University Hospital, Granada, Spain

ARTICLE INFO

Article history:
Received 13 July 2011
Received in revised form 11 October 2011
Accepted 29 October 2011
Available online 21 November 2011

Keywords:
Schizophrenia
Infection
Meta-analysis

ABSTRACT

Schizophrenia is a highly disabling and limiting disorder for patients and the possibility that infections by some microorganisms may be associated to its development may allow prevention and recovery. In the current study we have done a meta-analysis of studies that have assessed the possible association between detection of different infectious agents and schizophrenia. We report results that support the idea that there is a statistically significant association between schizophrenia and infection by Human Herpesvirus 2 (OR = 1.34; CI 95%: 1.09–1.70; $p = 0.05$), Borna Disease Virus (OR = 2.03; CI 95%: 1.35–3.06; $p < 0.01$), Human Endogenous Retrovirus W (OR = 19.31; CI 95%: 6.74–55.29; $p < 0.001$), *Chlamydophila pneumoniae* (OR = 6.34; CI 95%: 2.83–14.19; $p < 0.001$), *Chlamydophila psittaci* (OR = 29.05; CI 95%: 8.91–94.70; $p < 0.001$) and *Toxoplasma gondii* (OR = 2.70; CI 95%: 1.34–4.42; $p = 0.005$). The implications of these findings are discussed and further research options are also explicated.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

Schizophrenia is considered a neurodevelopmental disorder, with an important genetic component (Jones and Murray, 1991; Tsuang, 2000), as proven by a higher incidence among patients' first degree family members (McGuffin et al., 1995). Recent studies have stated the implication of several genes in the development of psychiatric disorders (Fatemi and Folsom, 2009), although there is no single genetic alteration that has been replicated in all studies (Levitt et al., 2006). On the other hand, many studies indicate that there must be other environmental factors that interact with genetic ones. Among these factors we may find exposure to toxic factors, stress or infections (Sullivan et al., 2003; Arseneault et al., 2004; Moore et al., 2007; Fatemi and Folsom, 2009). Thus, some authors suggest that schizophrenia might be caused, at least in a subgroup of patients, by congenital alterations which take place during neurodevelopment (Tandon et al., 2008). These alterations could result from possible environmental factors, particularly infections occurring during prenatal and perinatal stages which may, in turn, have neuropsychiatric consequences, including irreversible neurological lesions, behavioural problems, mental retardation, learning disabilities, mood alterations or psychotic symptoms (Brown, 2008). This hypothesis is based on epidemiological evidence showing that prenatal or perinatal exposure to different infectious agents, including *Toxoplasma gondii*, Cytomegalovirus, *Chlamydia* spp., and all types of Human Herpes Virus or Influenza, is associated to an increased risk for adult schizophrenia (Brown et al., 2004; Fellerhoff et al., 2005; Brown, 2006; Fellerhoff et al., 2007; Hammond and Hobbs, 2007; Dalman et al., 2008; Niebuhr et al., 2008). Certain genes associated with schizophrenia, including those also concerned with neurophysiology, are intimately related to the life cycles of these pathogens (Carter, 2009).

The possibility that there is an association between some microorganisms and the development of schizophrenia could provide means to improve both prevention and treatment.

In spite of the great variety of studies, results have been in most cases contradictory (Coffey and Jessop, 1955; Leck, 1963; Selten et al., 1999; Brown et al., 2000; Limosin et al., 2003). Hence, this study sets out to thoroughly analyse and systematically up-to-date evidence for significant associations between a variety of infections and schizophrenia.

2. Method

The meta-analysis has a qualitative (systematic review) and a quantitative component. The systematic review is an epidemiologic description of the papers that regards the individual studies as study "subjects". Thus, we performed a systematic search of all articles published in English, Spanish or French in journals indexed on

* Corresponding author at: Department of Microbiology, School of Medicine, Avd de Madrid, 11, E-18012 Granada, Spain. Tel.: +34 958242071; fax: +34 958246119.
E-mail address: asp@ugr.es (A. Sorlozano).

0920-9964/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2011.10.026

MEDLINE, *Psychinfo*, *Isi Web of Knowledge* and *Cochrane Library* up to December 2010. The search terms used were "Schizophrenia" or Schizophrenia*, "Viruses" or Virus*, "Bacteria" or Bacteria*, "Fungi" or Fungi*, and "Parasites" or Parasites*. After that search, we excluded from our study sample a group of papers including non-controlled cohort studies, reviews, studies which did not present their results in a correct and/or explicit manner, animal studies, studies where the control group was made up of patients with other psychiatric or neurological disorders, and those that did not assess the infectious processes and risk factors for the disorder were excluded from our meta-analysis. On the other hand, studies included were those that examined patients and healthy controls (characterized by absence of psychiatric disorders or any neurological disease), cohort studies of patients and controls, and case series. It was required that schizophrenic patients were included in the studies, and that the aim of the study was the direct or indirect search of some microorganism trying to establish a possible association between infection and schizophrenia.

The quantitative component of the meta-analysis refers to the statistical grouping of the results, in which we obtain a single-effect estimate combining the observed effects in the different individual studies. The following data were obtained for each serologic or molecular determination in each publication: odds ratios (OR) and their 95% confidence intervals (CI), population weights and statistical significance of the analyses.

The DerSimonian and Laird (1986) method was used as it produces overall estimates that are less affected by heterogeneity among studies. Heterogeneity among studies was determined using Cochran's Q statistic method when the number of papers included was equal or more than five. Additionally, Higgins I^2 was also used as a measure of total OR variability given heterogeneity among studies. Hence, very high values of the latter measure, above 75%, would indicate a strong heterogeneity suggesting the need to carry out an additional meta-regression using the Restricted Maximum Likelihood (REML) method. In such cases, we also performed a more detailed sub-analysis of the different subgroups, when the number of studies to be included in each subgroup was big enough (equal to or greater than three). As a whole, we considered that no relationship existed between exposure to microorganisms and the presence of schizophrenia when the CI at 95% included the one unit value (Egger et al., 1995).

Begg's (Begg and Mazumbar, 1994) and Egger's (Egger et al., 1997) tests were used when the number of studies included was equal to or larger than five, in order to check for any particular publication biases and their magnitude. Studies' quality was assessed using the Newcastle-Ottawa Quality Assessment Scale (Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm; updated 10 February 2010). Data obtained from the various studies were analysed using the STATA Release 10.1 statistical package.

3. Results

Table 1 shows the results of the meta-analysis that finally included 56 studies after taking into account the above-described inclusion criteria.

3.1. Herpesviridae family

The combined OR estimation of the eleven studies that compared detection of different markers for infection by Human Herpesvirus-1 (HHV-1) between schizophrenic patients and healthy controls was 1.37 (CI 95%: 0.78–2.39; $p=0.273$). When heterogeneity tests were done on the results, we obtained a value of $\chi^2_{exp}=11.69$, with 10 degrees of freedom and $p=0.306$, after which we could state that the differences found between the studies were due to randomness. This was also corroborated by coefficient $I^2=14.5\%$, which indicated that only 14.5% of the variability of the ORs was due to the heterogeneity of the studies. In spite of the absence of important and non-significant heterogeneity (<75%), a detailed study using meta-regression was carried out on the effect of some factors on the overall OR value. Hence, it was concluded that the technique used to detect HHV-1 infection did not seem to affect OR value ($p=0.897$); thus, there was no reason to state that the OR values obtained from studies that detected DNA using brain tissue (OR = 1.15, CI 95%: 0.23–5.80) were significantly different from the OR values coming from studies in which serum antibodies were used (OR = 1.14, CI 95%: 0.73–1.79). Begg's test was not significant ($p=1.000$) and this indicated that there was a potential publishing bias. A similar result was obtained after Egger's test ($p=0.774$). The quality of the studies examined was medium-high, and it was higher in the more recent studies due to the introduction of quality validation scales, a fact that favoured the control of the data included in the articles.

Six studies compared the exposure to Human Herpesvirus-2 (HHV-2) in schizophrenic patients versus healthy controls. Studies were heterogeneous and the most relevant ones were those by Mortensen et al. (2010) and by Buka et al. (2008) due to their comparatively large sample size which confers them a higher weight and importance. When all six studies were combined, we obtained an overall OR of 1.34 (CI 95%: 1.09–1.70; $p=0.05$) for the association between HHV-2 and schizophrenia. When we performed heterogeneity tests on the results, we obtained a $\chi^2_{exp}=4.27$ value, with 5 degrees of freedom and $p=0.511$, which allowed us to confirm that the differences found between the studies could be due to randomness. There was no evident publishing bias, as the Begg's and Egger's tests were not significant ($p=0.452$ and $p=0.341$, respectively).

There were four studies that compared infection by Varicella Zoster Virus (VZV), through IgG or viral DNA, in schizophrenia patients versus healthy controls. The weight of the studies was very similar (ranging from 24.66% to 25.36%), with a small sample size in all four studies and an acceptable quality. Significant OR values were not found for any of the studies or, indeed, after calculating combined OR estimations (OR = 1.17; CI 95%: 0.16–8.58; $p=0.877$).

No significant global estimation was found (OR = 1.67; CI 95%: 0.57–4.94; $p=0.352$) when we analysed the five studies that compared the infection by Epstein-Barr Virus (EBV) in schizophrenia patients versus healthy controls. The absence of positive results was remarkable, both in cases as in controls, in the studies done with brain tissue samples, as also observed in all previous studies. The study with the highest weight was that by DeLisi et al. (1986). When we performed heterogeneity tests, we obtained a value of $\chi^2 exp=4.29$, with 4 degrees of freedom and $p=0.306$, which suggests that the differences found between the studies could be due to randomness, as further corroborated by an I^2 coefficient of 31.6%. Begg's and Egger's tests were not significant ($p=0.865$ and $p=0.324$, respectively) indicating no evidence of publication bias.

We included in our meta-analysis fifteen studies that considered infection by Cytomegalovirus (CMV) as a risk factor for schizophrenia. The studies that stood out the most, due to their weight, were those by Brown et al. (2006) and Albrecht et al. (1980), representing 26.58% and 22.11% of the total sample. Additionally, the highest quality was found on the following studies: Brown et al. (2006), Fukuda et al. (1999) and Taller et al. (1996). After combining all fifteen studies no significant overall association between infections by CMV and schizophrenia ($p=0.544$) was found (OR = 0.86; CI 95%: 0.54–1.38). After heterogeneity tests, a value of $\chi^2_{exp}=12.81$ with 14 degrees of freedom, and $p=0.541$, suggested that the differences found between the studies could be due to randomness. It was striking to find that seven of the studies were performed on post mortem brain tissue samples and that none of them found positive results, except for the study by Moises et al. (1988). In spite of the absence of heterogeneity, a detailed study of the effect of some factors on the value of the OR via meta-regression was carried out, and it was

Table 1
Analysis and evaluation of studies included in the meta-analysis.

Microorganism	Study	Sample	Technique	Determination	Descriptive statistics				Inferential statistics			Quality			Global OR
					Cases		Controls		OR	95% CI	Weight (%)	S	C	E	
					Pos	Neg	Pos	Neg							(95% CI; p value)
HHV-1	Prasad et al. (2007)	SE	ELISA	IgG	15	15	8	36	4.50	1.58–12.84	22.57	***	**	*	1.37
	Brown et al. (2006)	SE	ELISA	IgG	41	19	70	40	1.23	0.63–2.41	27.18	****	**	*	(0.78–2.39;
	Conejero-Goldberg et al. (2003)	BR	N-PCR	DNA	0	14	0	26	1.83	0.03–97.01	1.69	***		*	$p=0.273$)
	Fukuda et al. (1999)	SE	ELISA	IgG	7	4	3	6	3.50	0.55–22.30	14.05	***	**	*	
	Taller et al. (1996)	BR	N-PCR	DNA	0	30	0	23	0.77	0.01–40.28	1.71	***	**	*	
	Alexander et al. (1992a)	BR	PCR	DNA	0	8	0	16	1.94	0.03–106.66	1.67	***		*	
	Carter et al. (1987)	BR	HIB	DNA	0	20	0	21	1.05	0.02–55.36	1.70	****		*	
	DeLisi et al. (1986)	SE	IFA	IgG	18	20	27	14	0.47	0.19–1.16	24.32	****		*	
	Taylor and Crow (1986)	BR	HIB	DNA	0	25	0	31	1.24	0.02–64.45	1.71	***		*	
	Stevens et al. (1984)	BR	IPA	Ag	0	25	0	16	0.65	0.01–34.23	1.70	***			
	Gotlieb-Stematsky et al. (1981)	SE	IFA	Ab	41	0	25	0	1.63	0.03–84.59	1.71	**		*	
HHV-2	Mortensen et al. (2010)	SE	ELISA	IgG	97	505	67	535	1.53	1.10–2.14	44.67	****	**	**	1.34
	Buka et al. (2008)	SE	ELISA	IgG	62	138	134	410	1.37	0.96–1.96	39.04	***	**	**	(1,09–1.70;
	Brown et al. (2006)	SE	ELISA	IgG	16	44	24	86	1.30	0.63–2.70	9.38	****	**	*	$p=0.05$)
	Conejero-Goldberg et al. (2003)	BR	N-PCR	DNA	0	14	0	26	1.83	0.03–97.01	0.32	***		*	
	DeLisi et al. (1986)	SE	IFA	IgG	17	21	24	17	0.57	0.23–1.40	6.28	****		*	
	Stevens et al. (1984)	BR	IPA	Ag	0	25	0	16	0.65	0.01–34.23	0.32	***			
VZV	Fukuda et al. (1999)	SE	ELISA	IgG	11	0	9	0	1.21	0.02–66.96	24.66	***	**	**	1.17
	Taller et al. (1996)	BR	N-PCR	DNA	0	30	0	23	0.77	0.01–40.28	25.36	***	**	**	(0.16–8.58;
	Alexander et al. (1992a)	BR	PCR	DNA	0	8	0	16	1.94	0.03–106.66	24.74	***		*	$p=0.877$)
	Carter et al. (1987)	BR	HIB	DNA	0	20	0	21	1.05	0.02–55.36	25.24	****		*	
EBV	Conejero-Goldberg et al. (2003)	BR	N-PCR	DNA	0	14	0	26	1.83	0.03–97.01	6.48	***		*	1.67 (0.57–4.94;
	Fukuda et al. (1999)	SE	ELISA	IgG	11	0	8	1	4.06	0.15–112.39	10.89	***	**	**	$p=0.352$)
	Taller et al. (1996)	BR	N-PCR	DNA	0	30	0	23	0.77	0.01–40.28	6.52	***	**	**	
	DeLisi et al. (1986)	SE	IFA	IgG	35	3	35	6	2.00	0.46–8.64	56.15	****		*	
	Gotlieb-Stematsky et al. (1981)	SE	IFA	Ab	39	2	24	1	0.81	0.07–9.45	19.96	**		**	
CMV	Brown et al. (2006)	SE	ELISA	IgG	43	17	73	37	1.28	0.64–2.55	26.58	****	**	*	0.86
	Conejero-Goldberg et al. (2003)	BR	N-PCR	DNA	0	14	0	26	1.83	0.03–97.01	1.27	***		*	(0.54–1.38; $p=0.544$)
	Fukuda et al. (1999)	SE	ELISA	IgG	8	3	7	2	0.76	0.10–5.96	9.31	***	**	**	
	Taller et al. (1996)	BR	N-PCR	DNA	0	30	0	23	0.77	0.01–40.28	1.28	***	**	**	
	Sierra-Honigmann et al. (1995)	BR	N-PCR	DNA	0	3	0	3	1.0	0.01–66.06	1.14	*		*	
	Alexander et al. (1992b)	BR	PCR	DNA	0	8	0	16	1.94	0.03–106.66	1.24	***		*	
	Moises et al. (1988)	BR	HIB	DNA	1	11	0	9	2.48	0.10–68.14	4.29	**		**	
	Carter et al. (1987)	BR	HIB	DNA	0	20	0	21	1.05	0.02–55.37	1.27	****		*	
	Rimon et al. (1986)	SE	ELISA	IgM	0	40	1	39	0.32	0.01–8.22	4.50	****		*	
	Shrikhande et al. (1985)	CSF	ELISA	IgG	0	20	4	6	0.03	0.00–0.74	4.96	***		*	
	Shrikhande et al. (1985)	CSF	ELISA	IgG	1	11	4	6	0.14	0.01–1.51	7.34	***		*	
	Stevens et al. (1984)	BR	IPA	Ag	0	25	0	16	0.65	0.01–34.23	1.27	***			
	Torrey et al. (1982)	CSF	ELISA	Ab	20	158	0	41	10.73	0.64–181.21	5.65	***			
	Albrecht et al. (1980)	CSF	ELISA	IgG	28	32	16	10	0.55	0.21–1.40	22.11	**		*	
	Albrecht et al. (1980)	SE	ELISA	IgG	57	3	15	1	0.76	0.07–7.67	7.81	**		*	
HHV-6	Conejero-Goldberg et al. (2003)	BR	N-PCR	DNA	0	14	1	25	0.59	0.02–15.34	38.16	***		*	0.34 (0.49–2.42;
	Fukuda et al. (1999)	SE	ELISA	IgG	8	3	9	0	0.13	0.01–2.85	42.21	***	**	**	$p=0.283$)
	Taller et al. (1996)	BR	N-PCR	DNA	0	30	0	23	0.77	0.01–40.28	19.63	***	**	**	
BDV	Na et al. (2009)	SE	IFA	Ab	0	60	0	60	1.00	0.02–51.22	1.04	****	**	**	2.03
	Na et al. (2009)	BL	RT-PCR	RNA	0	60	0	60	1.00	0.02–51.22	1.04	****	**	**	(1.35–3.06;
	Nunes et al. (2008)	BL	RT-PCR	RNA	12	15	4	23	4.60	1.25–16.97	6.46	**	**	**	$p<0.01$)
	Terayama et al. (2003)	SE	WB	Ab	7	25	1	24	6.72	0.77–58.79	3.02	*		*	
	Lebain et al. (2002)	SE	IFA	Ab	8	55	45	245	0.79	0.35–1.77	10.74	***		**	
	Fukuda et al. (2001)	BL	RT-PCR	RNA	0	45	0	45	1.0	0.02–51.49	1.04	**		*	
	Fukuda et al. (2001)	SE	WB	Ab	18	27	5	40	5.33	1.77–16.10	7.91	**		*	
	Fukuda et al. (2001)	SE	ECLIA	Ab	0	45	1	44	0.33	0.01–8.22	1.50	**		*	
	Nakamura et al. (2000)	BR	RT-PCR	RNA	1	3	0	2	2.14	0.06–77.54	1.23	**		*	
	Selten et al. (2000)	SE	IFA	Ab	3	26	6	20	0.38	0.09–1.73	5.33	**		**	
	Selten et al. (2000)	BL	RT-PCR	RNA	4	25	9	17	0.30	0.08–1.14	6.30	**		**	
	Chen et al. (1999a)	SE	WB	Ab	38	276	16	343	2.95	1.61–5.40	13.09	***	**	**	
	Chen et al. (1999b)	BL	RT-PCR	RNA	11	63	7	127	3.17	1.17–8.56	8.85	***	**	**	
	Czygan et al. (1999)	BR	RT-PCR	RNA	0	13	0	52	3.89	0.07–205.08	1.03	**	*	**	
	Yamaguchi et al. (1999)	SE	ECLIA	Ab	26	819	10	907	2.88	1.30–3.14	11.54	****	**	**	
	Iwata et al. (1998)	BL	RT-PCR	RNA	3	74	2	82	1.66	0.27–10.22	4.02	**	**	**	
	Kubo et al. (1997)	SE	WB	Ab	2	177	0	70	1.99	0.09–41.89	1.81	****		**	
	Iwahashi et al. (1997)	BL	RT-PCR	RNA	6	61	0	26	5.60	0.30–103.06	1.87	**		**	
	Iwahashi et al. (1997)	SE	WB	Ab	12	55	0	26	11.94	0.68–209.34	1.66	**		**	

Table 1 (*continued*)

Microorganism	Study	Sample	Technique	Determination	Descriptive statistics				Inferential statistics			Quality			Global OR
					Cases		Controls		OR	95% CI	Weight (%)	S	C	E	
					Pos	Neg	Pos	Neg							(95% CI; *p* value)
	Richt et al. (1997)	SE	WB	Ab	2	8	0	10	6.18	0.26–146.77	1.55	**	**	**	
	Sierra-Honigmann et al. (1995)	BR	RT-PCR	RNA	0	3	0	3	1.00	0.01–66.06	0.92	*		*	
	Waltrip et al. (1995)	SE	IFA	Ab	13	75	3	17	1.13	0.29–4.36	6.19	****		*	
	Waltrip et al. (1995)	SE	WB	Ab	13	77	0	20	7.14	0.41–125.25	1.87	****		*	
HERV	Huang et al. (2006)	BL	RT-PCR	RNA	20	38	0	38	41.0	2.39–702.27	20.78	****	**	**	3.66
	Lillehoj et al. (2000)	SE	ELISA	Ab	25	13	10	17	3.27	1.17–9.15	54.79	***		*	(0.79–16.95;
	Coggiano et al. (1991)	BL	CO-C	RT-A	0	15	0	9	0.61	0.01–33.54	12.19	****		**	$p=0.097$)
	Feenstra et al. (1989)	BL	CO-C	RT-A	0	17	0	10	0.60	0.01–32.56	12.24	**		**	
HERV-W	Huang et al. (2010)	BL	RT-PCR	RNA	42	76	0	106	118.33	7.17–1952.77	11.90	***	**	**	19.31
	Perron et al. (2008)	SE	ELISA	Ag (env)	23	26	1	45	39.81	5.08–312.18	19.47	***	**	*	(6.74–55.29;
	Perron et al. (2008)	SE	ELISA	Ag (gag)	24	25	2	44	21.12	4.60–96.93	29.39	***	**	*	$p<0.001$)
	Karlsson et al. (2004)	SE	RT-PCR	RNA	9	45	2	44	4.40	0.90–21.52	27.92	*		*	
	Karlsson et al. (2001)	CSF	RT-PCR	RNA	10	25	0	30	25.12	1.40–449.86	11.33	****	**	*	
HTLV-1	Kubo et al. (1997)	SE	HA	Ab	9	170	6	64	0.56	0.19–1.65	93.16	****		**	0.58
	Taller et al. (1996)	BR	RT-PCR	RNA	0	30	0	23	0.77	0.01–40.28	6.84	***	**	**	(0.20–1.62; $p=0.297$)
Influenza virus	Taller et al. (1996)	BR	RT-PCR	RNA	0	30	0	23	0.77	0.01–40.28	12.11	***	**	**	1.01
	Sierra-Honigmann et al. (1995)	BR	RT-PCR	RNA	0	3	0	3	1.0	0.01–66.06	10.79	*		*	(0.26–4.01; $p=0.986$)
	Albrecht et al. (1980)	CSF	ELISA	Ab	55	5	24	2	0.92	0.17–5.06	64.93	**		**	
	Albrecht et al. (1980)	CSF	ELISA	Ab	60	0	26	0	2.28	0.04–118.15	12.17	**		**	
C. trachomatis	Fellerhoff et al. (2007)	BL	PCR	DNA	0	72	4	221	0.34	0.02–6.38	48.47	**	**	**	4.39
	Fellerhoff et al. (2005)	BL	PCR	DNA	3	7	1	114	48.86	4.48–532.35	51.53	**	**	**	(0.03–571.24; $p=0.551$)
C. pneumoniae	Fellerhoff et al. (2007)	BL	PCR	DNA	11	61	8	217	4.89	1.88–12.70	71.44	**	**	**	6.34
	Fellerhoff et al. (2005)	BL	PCR	DNA	4	6	6	109	12.11	2.68–54.75	28.56	**	**	**	(2.83–14.19; $p<0.001$)
C. psittaci	Fellerhoff et al. (2007)	BL	PCR	DNA	13	59	2	223	24.57	5.39–111.89	60.73	**	**	**	29.05
	Fellerhoff et al. (2005)	BL	PCR	DNA	4	6	2	113	37.67	5.72–248.22	39.27	**	**	**	(8.91–94.70; $p<0.001$)
T. gondii	Tamer et al. (2008)	SE	ELISA	Ab	16	24	5	32	4.27	1.37–13.28	12.55	**	**	*	2.70
	Niebuhr et al. (2008)	SE	ELISA	Ab	15	165	37	495	1.22	0.65–2.27	16.15	****	**	***	(1.34–4.42;
	Mortensen et al. (2007)	SE	ELISA	Ab	60	197	171	511	0.91	0.65–1.27	17.73	****	**	**	$p=0.005$)
	Cetinkaya et al. (2007)	SE	ELISA	Ab	66	34	11	39	6.88	3.13–15.11	15.05	**	*	**	
	Alvarado-Esquivel et al. (2006)	SE	ELISA	Ab	5	15	16	164	3.42	1.10–10.63	12.55	***	**	*	
	Alvarado-Esquivel et al. (2006)	SE	ELISA	Ab	5	13	16	164	3.94	1.25–12.48	12.43	***	**	*	
	Conejero-Goldberg et al. (2003)	BR	N-PCR	DNA	0	14	0	26	1.83	0.03–97.01	2.58	***		*	
	Yolken et al. (2001)	SE	ELISA	Ab	14	24	3	24	4.67	1.19–18.35	10.95	****	**	**	
Parvovirus B19	Hobbs (2006)	BR	N-PCR	DNA	3	32	5	30	0.56	0.12–2.56			**	**	$p=0.457$
Parvovirus AAV-2	Hobbs (2006)	BR	PCR	DNA	1	34	5	30	0.18	0.02–1.58			**	**	$p=0.123$
JC virus	Carter et al. (1987)	BR	PCR	DNA	0	20	0	21	1.05	0.02–55.37		****		*	$p=0.987$
BK virus	Carter et al. (1987)	BR	PCR	DNA	0	20	0	21	1.05	0.02–55.37		****		*	$p=0.987$
HERV-K115	Otowa et al. (2006)	BL	PCR	DNA	15	163	17	164	0.89	0.43–1.84		***	**	*	$p=0.748$
HIV	Hart et al. (1999)	SE	WB	Ab	19	22	4	12	3.47	0.96–12.59		***		**	$p=0.058$
Toxocara spp.	Kaplan et al. (2008)	SE	ELISA	Ab	45	53	2	98	41.60	9.71–178.30		***	**	*	$p<0.0001$

SE: serum; BR: biopsy of brain tissue; CSF: cerebrospinal fluid; BL: blood; PCR: polymerase chain reaction; N-PCR: nested-polymerase chain reaction; RT-PCR: reverse transcriptase polymerase chain reaction; HIB: hybridization; ELISA: enzyme-linked immunoSorbent assay; WB: western blot; ECLIA: electrochemiluminescence immunoassay; IFA: immunofluorescence assay; IPA: immunoperoxidase assay; RT-A: RT activity; HA: hemagglutination; DNA: deoxyribonucleic acid; RNA: ribonucleic acid; IgG: immunoglobulin G; IgM: immunoglobulin M; Ag: antigen; Ab: antibody; Pos: positive; Neg: negative; S: Selection; C: Comparability; E: Exposur.
Asterisks indicate the level of study quality: from low quality (*) to (****) high quality.

found that the technique used to detect CMV infection did not seem to affect the value of OR ($p=0.728$). Therefore, we found no reason to state that OR obtained from studies using DNA from brain tissue (OR = 1.30, CI 95%: 0.30–5.62) was significantly different from the OR obtained using the studies in which antibodies were detected using serum or cerebrospinal fluid (OR = 1.55, CI 95%: 0.32–2.28). Begg's and Egger's tests were not significant ($p=0.428$ and $p=0.628$, respectively), indicating that there was no publishing bias.

Finally, three studies comparing infection by Human Herpesvirus-6 (HHV-6) were included, all of them of acceptable quality. The statistical analysis could not confirm the existence of a significant association between infection by this virus and schizophrenia (OR = 0.34; CI 95%: 0.49–2.42; $p=0.283$).

3.2. Borna Disease Virus (BDV)

This is the most widely studied relationship between an infectious agent and schizophrenia. We included 23 studies in the present meta-analysis, 3 of which stood out as those of highest weight and quality: Yamaguchi et al., 1999; Chen et al., 1999a, 1999b. The estimated combined OR was 2.03 (CI 95%: 1.35–3.06; $p<0.01$), indicating a true association between schizophrenia and BDV infection. Having performed heterogeneity studies between the studies, the result was $\chi^2_{exp}=32.70$ with 22 degrees of freedom ($p=0.086$) indicating that there is a trend for significant heterogeneity among OR values obtained from different studies. This was also suggested by a I^2 coefficient value of 29.7%, which indicates that 29.7% of the variability between the OR values obtained from different studies was due to the

heterogeneity between them, i.e., there is some heterogeneity, although not too high. We also performed here a detailed study of the effect of some factors on the overall OR value using meta-regression. Hence, we found that the technique used to detect BDV infection did not seem to influence OR value ($p=0.812$). Thus, there was no reason to state that OR of the studies that detected RNA from blood or brain tissue (OR = 1.99, CI 95%: 0.96–4.13) was significantly different from the OR values obtained in studies in which serum antibodies were detected (OR = 2.11, CI 95%: 0.95–4.79). Begg's and Egger's tests were also performed and they were not significant ($p=0.130$ and $p=0.941$, respectively), indicating no publication bias.

3.3. Human Endogenous Retroviruses (HERVs)

Four studies compared infection by HERVs in patients with schizophrenia versus healthy controls. Among them, the study by Huang et al. (2006) was the one with the highest quality, also presenting the most significant estimated OR, although its CI 95% was wide. The study with the heaviest weight (54.79%) was the one by Lillehoj et al. (2000), which also presented a significant OR, indicating association between gene activation or protein expression of HERVs and disorder. In spite of these results, having combined all the articles, we only found a marginal significance between HERVs and schizophrenia ($p=0.097$), with a combined OR of 3.66, with a CI 95% of 0.79–16.95.

The association between HERV-W and schizophrenia was assessed in five studies with similar sample sizes. With the exception of the study by Karlsson et al. (2004), which was the one with the lowest quality according to the NOS scale, the other four presented a significantly positive estimated OR. The combined OR was significant (OR = 19.31; CI 95%: 6.74–55.29; $p<0.001$), which allowed us to state that gene activation or protein expression of HERV-W could be a risk factor for schizophrenia. When we performed heterogeneity tests we obtained a value of $\chi^2_{exp}=5.42$, with 4 degrees of freedom and $p=0.247$, which allows us to say that the differences found between the studies could be due to randomness; this was corroborated by a I^2 coefficient of 26.2%. Begg's and Egger's tests were not significant ($p=0.806$ and $p=0.245$, respectively) indicating no publication bias.

3.4. Human T-cell Lymphotropic Virus (HTLV-1)

Only two studies with acceptable quality were found about the possible relationship between HTLV-1 and schizophrenia. The individual ORs of the studies were not significant, and neither was the combined OR (OR = 0.58, CI 95%: 0.20–1.62; $p=0.297$).

3.5. Influenza virus

None of the four studies included in the meta-analysis found a significant association.

3.6. Chlamydiaceae family

Both studies included (Fellerhoff et al., 2005, 2007) are of similar quality and used blood samples to detect bacterial DNA through polymerase chain reaction (PCR). In the case of *C. trachomatis*, no statistical association was observed between the infection and the disorder (OR = 4.39; CI 95%: 0.03–571.24; $p=0.551$), although an association was found for *Chlamydophila pneumoniae* (OR = 6.34; CI 95%: 2.83–14.19; $p<0.001$) and for *Chlamydophila psittaci* (OR = 29.05; CI 95%: 8.91–94.70; $p<0.001$).

3.7. Toxoplasma gondii

Eight studies centred on the possible relationship between *T. gondii* and schizophrenia, comparing the detection of infection markers by this protozoon in a sample of patients and healthy controls. All these studies had similar weights, except for the one by Conejero-Goldberg et al. (2003) that used post-mortem brain tissue samples and included, because of this, a smaller number of cases and controls; this study was also of lower quality according to the NOS scale. Due to their large sample size the studies by Niebuhr et al. (2008) and Mortensen et al. (2007) stood out, the former being of the highest quality. The latter obtained the narrowest CI 95% range due to the large amount of participants included. After combining the different studies, we found a significant association between parasitation by *T. gondii* and schizophrenia ($p=0.005$); the combined OR was 2.70, with a CI 95% of 1.34–4.42. We can therefore state that schizophrenia was 2.7 times more frequent in people in whom the marker for *T. gondii* was found than in people in whom it was not detected. When only studies that used the *T. gondii* infection marker in serum antibodies were included, the result continued to be statistically significant with an OR = 2.74 (CI 95%: 1.33–5.62; $p=0.006$). When heterogeneity tests were performed between the studies, a significant value was obtained: $\chi^2_{exp}=33.89$ with 7 degrees of freedom, $p<0.001$. This result is in accordance with the coefficient $I^2=79.3\%$, which indicates that 79.3% of the variability of the ORs is due to the heterogeneity of the studies analysed. The heterogeneity of the studies (>75%) was due to the fact that the OR reported in the only publication that detected *T. gondii* DNA in brain biopsies (OR = 1.83, CI 95%: 0.03–97.01) was significantly different ($p<0.001$) from that of research that detected serum antibodies (OR = 2.74, CI 95%: 1.33–5.62). Finally, even though Begg's test was not significant ($p=0.711$), Egger's test was ($p=0.045$), which indicated a tendency to publish studies where results were significant, according to this last test.

3.8. Other infectious agents

Finally, Table 1 also shows the results for diverse individual studies that analysed the relationship between different infectious agents (parvovirus B19, parvovirus AAV-2, JC virus, BK virus, HERV-K115, HIV and *Toxocara* spp.) and schizophrenia.

4. Discussion

Despite numerous studies analysing the association between HHV-1 and schizophrenia, only one reported significant results (Prasad et al., 2007). In general, studies about this viral infection based on serological tests are just descriptive studies showing the prevalence of IgG in cases and controls, while studies using brain tissue samples have tried to determine whether the presence of the virus in the brain cells is associated with schizophrenia. However, no conclusive results on the potential association have been obtained. This can be due to some limitations of studies using brain tissue samples: the infection may reside in brain areas different to those assessed, the virus may be found in amounts too small to be detected by current techniques or conservation liquids may alter the brain tissue, because the samples used are frequently provided by tissue banks (Carter et al., 1987; Taller et al., 1996; Conejero-Goldberg et al., 2003).

Two of the studies exploring the association between infection by HHV-2 and schizophrenia were prospective cohort studies with pregnant women (Brown et al., 2006; Buka et al., 2008) assessing the presence of IgG in maternal serum. Genital infection with this virus may favour the infection of the newly born child during birth (Buka et al., 2001), a very severe infection, due to the immaturity of the child's immune system. Resulting brain lesions may explain the development of schizophrenia. Another possible hypothesis is that the

presence of anti-HHV-2 antibodies in the placenta could also indirectly cause damage to the developing brain, with no need for direct brain infection. Mortensen et al. (2010) used blood from newly born babies in the 4th to 7th days after birth and assumed that the antibodies found came from the mother, through the placenta. Our reported combined significant association between this virus and schizophrenia is strongly dependent of the association reported by Mortensen et al. (2010), the study with the largest sample size and the only one to report a positive association among the ones included in our analysis. This points out toward a small, yet significant, effect of the virus which is detectable only if a sufficiently large sample is used.

Regarding VZV, chickenpox in children has been shown to produce neurological damage as viral encephalitis (Riaza Gómez et al., 1999; Ziebold et al., 2001). The transmission of the infection through the placenta is rarely associated to defects in the newly born (Dufour et al., 1996), and the biggest risk for developing a severe clinical manifestation occurs when the mother is infected around four days before giving birth (Smith and Arvin, 2009). We interpret that the lack of association between schizophrenia and this virus could partly be due to the use of brain tissue samples for the detection of viral DNA which has provided negative results in all participants assessed by such method, as shown in Table 1. To have definite results, a prospective follow-up study should be carried out on newly born children whose mothers contracted chickenpox a few days before giving birth or in participants who have suffered viral encephalitis, with the aim of testing whether that associates with later development of schizophrenia.

Neurological complications due to EBV-infection are rare and usually benign; none of the studies that considered its association with schizophrenia obtained significant results.

Cytomegalovirus is a ubiquitous virus, with a very high prevalence, especially in low socio-economic populations (Cannon and Davis, 2005); therefore, it is not unusual to find significant differences between healthy controls and patients (Albrecht et al., 1980; Rimon et al., 1986; Fukuda et al., 1999; Brown et al., 2006). It is one of the main viruses involved in the appearance of brain lesions in foetuses and newly born children (Malm and Engman, 2007). Infection by CMV in the first stages of gestation is potentially teratogenic, because it interferes with the migration of brain cells (McCarthy et al., 2000). The affinity of CMV for the CNS reduces after birth, so if there was a relationship between schizophrenia and this virus, it would probably be due to a congenital infection. We did not find an association between this virus and schizophrenia. In any case, none of the studies included in this meta-analysis was a prospective cohort study which would be, in our opinion, the most adequate design to assess the development of schizophrenia in participants whose mothers suffered infection by CMV during pregnancy causing lesions to the baby's CNS.

Borna Disease Virus is an RNA virus exclusive to mammals in Central Europe, North America and some regions in Asia, but its extension is thought to be broader (Hatalski et al., 1997). BDV mainly infects the limbic system and the cerebellum, which play an important role in psychiatric disease. In animals, the infection produces behavioural disorders, which resemble certain neuropsychiatric disorders found in humans, like bipolar disorder or schizophrenia (de la Torre, 1994). The possible relationship between an infection by this virus and the appearance of mental disorders in humans has turned it into a particularly interesting infectious agent. There is certain controversy about the pathogenicity of BDV, which some authors have tried to clarify in numerous studies using different populations and diverse techniques (Ludwig et al., 1988; Bode et al., 2001; Bode, 2008; Scholbach and Bode, 2008). According to these authors, BDV is scarcely pathogenic, possibly producing subclinical or latent infections that could generate alterations in neurotransmitters. It should be noted that some authors have recently proven persistent seropositivity of this virus in a high percentage of psychiatric patients, which would suggest the possibility of a chronic infection with this virus in this type of patients (Heinrich and Adamaszek, 2010). Yamaguchi et al. (1999) used an electroluminescent technique to detect proteins p40 and p24 in human serum and concluded that infection by this virus was significantly more frequent among schizophrenic patients. This technique is highly sensitive, but not without its limitations, as Fukuda et al. (2001) were not able to detect any positivity using it but could detect them using Western blot technique. The studies by Chen's group also obtained positive results, using both Western blot techniques (Chen et al., 1999a) and RT-PCR (Chen et al., 1999b), although a negative report also exist (Na et al., 2009).

It is estimated that 8% of the human genome is made up of sequences of retroviral origin very different among them, which remains of infections that occurred early in human evolution (Blikstada et al., 2008). These are known as Human Endogenous Retroviruses (HERVs), which are part of the human genome and exhibit gene-like behaviour participating in some routine cell functions. However, their potential association with certain diseases such as multiple sclerosis, systemic lupus erythematosus or schizophrenia, has also been posed (Voisset et al., 2008). Its pathogenicity has been suggested as determined by interactions between hereditary and environmental factors (Christensen, 2010). Both Coggiano et al. (1991) and Feenstra et al. (1989) based their studies about the relationship of these retroviruses and schizophrenia on the demonstration of the activity of the reverse transcriptase in the lymphocytes of peripheral blood, with no success. Some years later, Lillehoj et al. (2000) considered these viruses capable of integrating and replicating alongside genomic DNA and able to exist as an exogenous form outside the accommodating cell. The most complete study, with highest quality among the ones included in this meta-analysis, was that by Huang et al. (2006), where they used RT-PCR to prove the presence of HERV RNA (gen *pol*) in peripheral blood of subjects recently diagnosed with schizophrenia. The combined analysis of all these studies did not, though, provide significant evidence of the relationship between the infection and the disorder.

HERV-W retroviruses are characterized by integration in the human genome, although they present inter- and intra-individual differences. Perron et al. (2008) obtained a statistically significant result, i.e., that viral antigens were found more often in schizophrenic participants (gag and env types). Karlsson et al. (2001, 2004) used PCR to detect the presence of HERV-W sequences in healthy controls and in first-episode schizophrenia patients. In their 2004 study, they used serum samples and no statistically significant differences were found, although significant ORs had been found in the 2001 study using CSF. We should highlight the study by Huang et al. (2010) that demonstrates that HERV-W transcriptional activation is associated with the development of schizophrenia in some patients and indicated that the expression of HERV-W env proteins regulates the expression of schizophrenia-associated genes such as BDNF, NTRK2, and DRD3. This is further supported by our finding of a global, yet modest, increase of risk for schizophrenia.

No study to date has proven a significant association between infection by HTLV-1 and psychiatric disorders including schizophrenia (DeLisi and Sarin, 1985; Robert-Guroff et al., 1985; Rodgers-Johnson et al., 1996; Taller et al., 1996; Kubo et al., 1997). Studies performed on populations with a high prevalence of this infection, like Japan (Kubo et al., 1997) or Jamaica (Rodgers-Johnson et al., 1996), have not shown significant associations either. Therefore, an association would be even less likely in populations with low prevalence, like the Spanish (Toro et al., 2005). Our results guide us to conclude that this retrovirus does not seem to be a risk factor for schizophrenia.

Maternal exposure to influenza virus during pregnancy has been posed as a potential risk factor for schizophrenia among the offspring. The most accepted pathogenic hypothesis is that this virus may exert deleterious effects on foetal brain in interaction with other environmental and possibly genetic factors (Ellman et al., 2009). Studies performed on brain tissue samples (Sierra-Honigmann et al., 1995; Taller et al., 1996) and CSF (Albrecht et al., 1980) have not reported

statistically significant results, i.e., there is no conclusive data indicating that the influenza virus could be found in schizophrenic patients' brains or CSF. The recent pandemic with a novel influenza A (H1N1) virus may provide some opportunities for future research in this field (Manjunatha, 2010). The study by Mednick et al. (1988) was the first to prove an increased risk for schizophrenia after exposure to Influenza virus A2 during the second term of pregnancy. This result was later confirmed by other studies (Barr et al., 1990; Sham et al., 1992; Brown et al., 2000; Limosin et al., 2003). We should note that all these studies are ecological, therefore, limited, because they do not assess the real presence of infection, neither in the mother or the foetus. Finally, two other studies (Crow and Done, 1992; Cannon et al., 1996) analysed infection markers of influenza virus in mothers, but found no causal relationship. The present meta-analysis included four studies and we also report no association between influenza virus and risk for schizophrenia.

Fellerhoff et al. (2005, 2007) state that it is not possible to prove that bacteria from the *Chlamydiaceae* family are pathogenic agents for schizophrenia, or that they affect the duration or severity of the disorder. However, it is true that bacterial DNA can be found more often in schizophrenic patients than in controls. The combined result indicates a potential association between schizophrenia and some members of this family but new studies with more participants are needed to optimally explore these associations.

Due to *T. gondii*'s well known neurotropism, there has also been a classical interest in discovering a possible causal relationship between this parasite and schizophrenia. The first study in psychiatric patients was published in 1953 (Kozar et al., 1953) but from then on many other studies have been performed. The most likely mechanism by which *T. gondii* could cause schizophrenia is by affecting neurotransmitters in brain areas known to be involved in this disorder (Yolken et al., 2009). Thus, astrocyte activation during toxoplasma infections increases kynurenic acid production in the brain, an effect which is greater in subjects that have high tryptophan dioxygenase activity, which, in turn, has been posed as linked to schizophrenia. Increased kynurenic acid levels in the brain cause excessive inhibition of glutamine and nicotine neurotransmitter receptors, which is believed to cause cognitive symptoms of schizophrenia (Schwarcz and Hunter, 2007; Costa da Silva and Langoni, 2009). All studies included in the present meta-analysis, except for one (Conejero-Goldberg et al., 2003), are based on the detection of antibodies. Considering all the studies together we obtained a significant result, with values very similar to those found by a previous meta-analysis by Torrey et al. (2007). Some authors consider that the association might be spurious as, in some cases, the infection could have occurred after the first episode as a limitation to the positive results or because the presence of IgG versus *T. gondii* could be due to bad hygienic habits in some patients. Nonetheless, according to the data obtained in our and other meta-analyses, it seems plausible that there is a causal relationship between infection by *T. gondii* and schizophrenia. However, some cautions have to be taken into account: (i) these studies detect antibodies, not DNA or *T. gondii* cysts directly, (ii) *T. gondii* antibodies are not detected in most patients with schizophrenia and (iii) if results are adjusted depending on the quality of the studies, there might be an overestimation of the combined OR values: i.e., studies with non significant ORs seemed to be of higher quality.

Finally, there are seven micro-organisms for which there is only one study that has addressed the possible association with schizophrenia (*parvovirus B19*, *parvovirus AAV-2*, *JC virus*, *BK virus*, *HERV-K115*, *HIV* and *Toxocara* spp.). These studies cannot be addressed in a meta-analysis. Considering that these studies are anecdotal, we were unable to draw definitive conclusions about their association with schizophrenia.

In conclusion, our systematic review and meta-analysis show that viruses have been the most frequently assessed infectious agents in relation to the development of schizophrenia. Among these, we found significant associations between schizophrenia and Human Herpesvirus 2, Borna Disease Virus and HERV-W. Among the bacteria examined, the detection of DNA in blood of *C. pneumoniae* and *C. psittaci* was also significantly more frequent among schizophrenic patients than in the control group, although this did not hold true for *C. trachomatis*. According to our methodology, there was also a statistically significant association between schizophrenia and *T. gondii*, although we found that there might be publication bias. As a whole, though, from the immunological point of view, it may be concluded that we found evidence that the detection of serum IgG antibodies versus *T. gondii* could be a factor significantly associated to schizophrenia. We recommend that new prospective and comparative studies, with sufficient sample power, should be undertaken to obtain more definite results. Such studies should use a combination of various microbiological techniques (simultaneously analysing blood, cerebrospinal fluid and brain tissue using standardized techniques and with an adequate sensitivity) and take into account whether the patient is undergoing an acute bout or a stable phase of the disorder.

Role of funding source

This study was conducted without any financial support.

Contributors

All authors contributed to subsequent revisions critically for important intellectual content, and to approval of the final version for publication.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

None.

References

Albrecht, P., Torrey, E.F., Boone, E., Hicks, J.T., Daniel, N., 1980. Raised Cytomegalovirus-antibody level in cerebrospinal fluid of schizophrenic patients. Lancet 2 (8198), 769–772.

Alexander, R.C., Cabirac, G., Lowenkopf, T., Casanova, M., Kleinman, J., Wyatt, R.J., et al., 1992a. Search for evidence of Herpes Simplex Virus, type 1, or Varicella-Zoster Virus infection in postmortem brain tissue from schizophrenic patients. Acta Psychiatr. Scand. 86 (5), 418–420.

Alexander, R.C., Spector, S.A., Casanova, M., Kleinman, J., Wyatt, R.J., Kirch, D.G., 1992b. Search for Cytomegalovirus in the postmortem brains of schizophrenic patients using the polymerase chain reaction. Arch. Gen. Psychiatry 49 (1), 47–53.

Alvarado-Esquivel, C., Alanis-Quinones, O.P., Arreola-Valenzuela, M.A., Rodriguez-Briones, A., Piedra-Nevarez, L.J., Duran-Morales, E., et al., 2006. Seroepidemiology of *Toxoplasma gondii* infection in psychiatric inpatients in a northern Mexican city. BMC Infect. Dis. 6, 178.

Arseneault, L., Cannon, M., Witton, J., Murray, R.M., 2004. Causal association between cannabis and psychosis: examination of the evidence. Br. J. Psychiatry 184, 110–117.

Barr, C.E., Mednick, S.A., Munk-Jorgensen, P., 1990. Exposure to influenza epidemics during gestation and adult schizophrenia. A 40-year study. Arch. Gen. Psychiatry 47 (9), 869–874.

Begg, C.B., Mazumbar, M., 1994. Operating characteristics of a rank correlation test for publication bias. Biometrics 50 (4), 1088–1101.

Blikstada, V., Benachenhoua, F., Sperberb, G.O., Blomberg, J., 2008. Evolution of Human Endogenous Retroviral sequences: a conceptual account. Cell. Mol. Life Sci. 65 (21), 3348–3365.

Bode, L., 2008. Human Bornavirus infection—towards a valid diagnostic system. APMIS Suppl. 124, 21–39.

Bode, L., Reckwald, P., Severus, W.E., Stoyloff, R., Ferszt, R., Dietrich, D.E., et al., 2001. Borna Disease Virus-specific circulating immune complexes, antigenemia, and free antibodies—the key marker triplet determining infection and prevailing in severe mood disorders. Mol. Psychiatry 6 (4), 481–491.

Brown, A.S., 2006. Prenatal infection as a risk factor for schizophrenia. Schizophr. Bull. 32 (2), 200–202.

Brown, A.S., 2008. The risk for schizophrenia from childhood and adult infections. Am. J. Psychiatry 165 (1), 7–10.

Brown, A.S., Schaefer, C.A., Wyatt, R.J., Goetz, R., Begg, M.D., Gorman, J.M., et al., 2000. Maternal exposure to respiratory infections and adult schizophrenia spectrum disorders: a prospective birth cohort study. Schizophr. Bull. 26 (2), 287–295.

Brown, A.S., Begg, M.D., Gravenstein, S., Schaefer, C.A., Wyatt, R.J., Bresnahan, M., et al., 2004. Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch. Gen. Psychiatry 61 (8), 774–780.

Brown, A.S., Schaefer, C.A., Quesenberry Jr., C.P., Shen, L., Susser, E.S., 2006. No evidence of relation between maternal exposure to Herpes Simplex Virus type 2 and risk of schizophrenia? Am. J. Psychiatry 163 (12), 2178–2180.
Buka, S.L., Tsuang, M.T., Torrey, E.F., Klebanoff, M.A., Bernstein, D., Yolken, R.H., 2001. Maternal infections and subsequent psychosis among offspring. Arch. Gen. Psychiatry 58 (11), 1032–1037.
Buka, S.L., Cannon, T.D., Torrey, E.F., Yolken, R.H., 2008. Maternal exposure to Herpes Simplex Virus and risk of psychosis among adult offspring. Biol. Psychiatry 63 (8), 809–815.
Cannon, M.J., Davis, K.F., 2005. Washing our hands of the congenital Cytomegalovirus disease epidemic. BMC Public Health 5, 70.
Cannon, M., Cotter, D., Coffey, V.P., Sham, P.C., Takei, N., Larkin, C., et al., 1996. Prenatal exposure to the 1957 influenza epidemic and adult schizophrenia: a follow-up study. Br. J. Psychiatry 168 (3), 368–371.
Carter, C.J., 2009. Schizophrenia susceptibility genes directly implicated in the life cycles of pathogens: Cytomegalovirus, Influenza, Herpes simplex, Rubella, and *Toxoplasma gondii*. Schizophr. Bull. 35 (6), 1163–1182.
Carter, G.I., Taylor, G.R., Crow, T.J., 1987. Search for viral nucleic acid sequences in the post mortem brains of patients with schizophrenia and individuals who have committed suicide. J. Neurol. Neurosurg. Psychiatry 50 (3), 247–251.
Cetinkaya, Z., Yazar, S., Gecici, O., Namli, M.N., 2007. Anti-*Toxoplasma gondii* antibodies in patients with schizophrenia-preliminary findings in a Turkish sample. Schizophr. Bull. 33 (3), 789–791.
Chen, C.H., Chiu, Y.L., Shaw, C.K., Tsai, M.T., Hwang, A.L., Hsiao, K.J., 1999a. Detection of Borna Disease Virus RNA from peripheral blood cells in schizophrenic patients and mental health workers. Mol. Psychiatry 4 (6), 566–571.
Chen, C.H., Chiu, Y.L., Wei, F.C., Koong, F.J., Liu, H.C., Shaw, C.K., et al., 1999b. High seroprevalence of Borna Virus infection in schizophrenic patients, family members and mental health workers in Taiwan. Mol. Psychiatry 4 (1), 33–38.
Christensen, T., 2010. HERVs in neuropathogenesis. J. Neuroimmune Pharmacol. 5 (3), 326–335.
Coffey, V.P., Jessop, W.J., 1955. Congenital abnormalities. Ir. J. Med. Sci. 6 (349), 30–48.
Coggiano, M.A., Alexander, R.C., Kirch, D.G., Wyatt, R.J., Kulaga, H., 1991. The continued search for evidence of retroviral infection in schizophrenic patients. Schizophr. Res. 5 (3), 243–247.
Conejero-Goldberg, C., Torrey, E.F., Yolken, R.H., 2003. Herpesviruses and *Toxoplasma gondii* in orbital frontal cortex of psychiatric patients. Schizophr. Res. 60 (1), 65–69.
Costa da Silva, R., Langoni, H., 2009. *Toxoplasma gondii*: host–parasite interaction and behavior manipulation. Parasitol. Res. 105 (4), 893–898.
Crow, T.J., Done, D.J., 1992. Prenatal exposure to influenza does not cause schizophrenia. Br. J. Psychiatry 161, 390–393.
Czygan, M., Hallensleben, W., Hofer, M., Pollak, S., Sauder, C., Bilzer, T., et al., 1999. Borna Disease Virus in human brains with a rare form of hippocampal degeneration but not in brains of patients with common neuropsychiatric disorders. J. Infect. Dis. 180 (5), 1695–1699.
Dalman, C., Allebeck, P., Gunnell, D., Harrison, G., Kristensson, K., Lewis, G., et al., 2008. Infections in the CNS during childhood and the risk of subsequent psychotic illness: a cohort study of more than one million Swedish subjects. Am. J. Psychiatry 165 (1), 59–65.
de la Torre, J.C., 1994. Molecular biology of Borna Disease Virus: prototype of a new group of animal viruses. J. Virol. 68 (12), 7669–7675.
DeLisi, L.E., Sarin, P.S., 1985. Lack of evidence for retrovirus infection in schizophrenic patients. Br. J. Psychiatry 146, 674–675.
DeLisi, L.E., Smith, S.B., Hamovit, J.R., Maxwell, M.E., Goldin, L.R., Dingman, C.W., et al., 1986. Herpes Simplex Virus, Cytomegalovirus and Epstein-Barr virus antibody titres in sera from schizophrenic patients. Psychol. Med. 16 (4), 757–763.
DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7 (3), 177–188.
Dufour, P., de Bievre, P., Vinatier, D., Tordjeman, N., Da Lage, B., Vanhove, J., Monnier, J.C., 1996. Varicella and pregnancy. Eur. J. Obstet. Gynecol. Reprod. Biol. 66 (2), 119–123.
Egger, M., Smith, G.D., Altman, D., 1995. Systematic Reviews in Health Care: Meta-analysis in Context, Second ed. BMJ Books, London.
Egger, M., Smith, G.D., Schneider, M., Zinder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315 (7109), 629–634.
Ellman, L.M., Yolken, R.H., Buka, S.L., Torrey, E.F., Cannon, T.D., 2009. Cognitive functioning prior to the onset of psychosis: the role of fetal exposure to serologically determined influenza infection. Biol. Psychiatry 65 (12), 1040–1047.
Fatemi, S.H., Folsom, T.D., 2009. The neurodevelopmental hypothesis of schizophrenia, revisited. Schizophr. Bull. 35 (3), 528–548.
Feenstra, A., Kirch, D.G., Bracha, H.S., Wyatt, R.J., 1989. Lack of evidence for a role of T-cell-associated retroviruses as an etiology of schizophrenia. Biol. Psychiatry 25 (4), 421–430.
Fellerhoff, B., Laumbacher, B., Wank, R., 2005. High risk of schizophrenia and other mental disorders associated with chlamydial infections: hypothesis to combine drug treatment and adoptive immunotherapy. Med. Hypotheses 65 (2), 243–252.
Fellerhoff, B., Laumbacher, B., Mueller, N., Gu, S., Wank, R., 2007. Associations between *Chlamydophila* infections, schizophrenia and risk of HLA-A10. Mol. Psychiatry 12 (3), 264–272.
Fukuda, R., Sasaki, T., Kunugi, H., Nanko, S., 1999. No changes in paired viral antibody titers during the course of acute schizophrenia. Neuropsychobiology 40 (2), 57–62.
Fukuda, K., Takahashi, K., Iwata, Y., Mori, N., Gonda, K., Ogawa, T., et al., 2001. Immunological and PCR analyses for Borna Disease Virus in psychiatric patients and blood donors in Japan. J. Clin. Microbiol. 39 (2), 419–429.
Gotlieb-Stematsky, T., Zonis, J., Arlazoroff, A., Mozes, T., Sigal, M., Szekely, A.G., 1981. Antibodies to Epstein-Barr virus, Herpes Simplex type 1, Cytomegalovirus and measles virus in psychiatric patients. Arch. Virol. 67 (4), 333–339.
Hammond, C.J., Hobbs, J.A., 2007. Parvovirus B19 infection of brain: possible role of gender in determining mental illness and autoimmune thyroid disorders. Med. Hypotheses 69 (1), 113–116.
Hart, D.J., Heath, R.G., Sautter Jr., F.J., Schwartz, B.D., Garry, R.F., Choi, B., et al., 1999. Antiretroviral antibodies: implications for schizophrenia, schizophrenia spectrum disorders, and bipolar disorder. Biol. Psychiatry 45 (6), 704–714.
Hatalski, C.G., Lewis, A.J., Lipkin, W.I., 1997. Borna disease. Emerg. Infect. Dis. 3 (2), 129–135.
Heinrich, A., Adamaszek, M., 2010. Anti-Borna disease virus antibody responses in psychiatric patients: long-term follow up. Psychiatry Clin. Neurosci. 64 (3), 255–261.
Hobbs, J.A., 2006. Detection of Adeno-associated Virus 2 and Parvovirus B19 in the human dorsolateral prefrontal cortex. J. Neurovirol. 12 (3), 190–199.
Huang, W.J., Liu, Z.C., Wei, W., Wang, G.H., Wu, J.G., Zhu, F., 2006. Human Endogenous Retroviral pol RNA and protein detected and identified in the blood of individuals with schizophrenia. Schizophr. Res. 83 (2–3), 193–199.
Huang, W., Li, S., Hu, Y., Yu, H., Luo, F., Zhang, Q., Zhu, F., 2010. Implication of the *env* gene of the Human Endogenous Retrovirus W family in the expression of BDNF and DRD3 and development of recent-onset schizophrenia. Schizophr. Bull. 37 (5), 988–1000.
Iwahashi, K., Watanabe, M., Nakamura, K., Suwaki, H., Nakaya, T., Nakamura, Y., et al., 1997. Clinical investigation of the relationship between Borna Disease Virus (BDV) infection and schizophrenia in 67 patients in Japan. Acta Psychiatr. Scand. 96 (6), 412–415.
Iwata, Y., Takahashi, K., Peng, X., Fukuda, K., Ohno, K., Ogawa, T., et al., 1998. Detection and sequence analysis of Borna Disease Virus p24 RNA from peripheral blood mononuclear cells of patients with mood disorders or schizophrenia and of blood donors. J. Virol. 72 (12), 10044–10049.
Jones, P., Murray, R., 1991. The genetics of schizophrenia is the genetics of neurodevelopment. Br. J. Psychiatry 158, 615–623.
Kaplan, M., Kalkan, A., Kuk, S., Demirdag, K., Ozden, M., Kilic, S.S., 2008. *Toxocara* seroprevalence in schizophrenic patients in Turkey. Yonsei Med. J. 49 (2), 224–229.
Karlsson, H., Bachmann, S., Schroder, J., McArthur, J., Torrey, E.F., Yolken, R.H., 2001. Retroviral RNA identified in the cerebrospinal fluids and brains of individuals with schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 98 (8), 4634–4639.
Karlsson, H., Schroder, J., Bachmann, S., Bottmer, C., Yolken, R.H., 2004. HERV-W-related RNA detected in plasma from individuals with recent-onset schizophrenia or schizoaffective disorder. Mol. Psychiatry 9 (1), 12–13.
Kozar, Z., Dłuzewski, L., Dłuzewska, A., Jaroszewski, Z., 1953. Toxoplasmosis and oligophrenia. Biul. Panstw. Inst. Med. Morsk. Trop. J. W. Gdansku. 5, 164–173.
Kubo, K., Fujiyoshi, T., Yokoyama, M.M., Kamei, K., Richt, J.A., Kitze, B., et al., 1997. Lack of association of Borna Disease Virus and human T-cell Leukemia Virus type 1 infections with psychiatric disorders among Japanese patients. Clin. Diagn. Lab. Immunol. 4 (2), 189–194.
Lebain, P., Vabret, A., Freymuth, F., Brazo, P., Chabot, B., Dollfus, S., et al., 2002. Borna Disease Virus and psychiatric disorders. Schizophr. Res. 57 (2–3), 303–305.
Leck, I., 1963. Incidence of malformations following influenza epidemics. Br. J. Prev. Soc. Med. 17, 70–80.
Levitt, P., Ebert, P., Mirnics, K., Nimgaonkar, V.L., Lewis, D.A., 2006. Making the case for a candidate vulnerability gene in schizophrenia: convergent evidence for regulator of G-protein signalling 4 (RGS4). Biol. Psychiatry 60 (6), 534–537.
Lillehoj, E.P., Ford, G.M., Bachmann, S., Schröder, J., Torrey, E.F., Yolken, R.H., 2000. Serum antibodies reactive with non-human primate retroviruses identified in acute onset schizophrenia. J. Neurovirol. 6 (6), 492–497.
Limosin, F., Rouillon, F., Payan, C., Cohen, J.M., Strub, N., 2003. Prenatal exposure to influenza as a risk factor for adult schizophrenia. Acta Psychiatr. Scand. 107 (5), 331–335.
Ludwig, H., Bode, L., Gosztonyi, G., 1988. Borna disease: a persistent virus infection of the central nervous system. Prog. Med. Virol. 35, 107–151.
Malm, G., Engman, M.L., 2007. Congenital Cytomegalovirus infections. Semin. Fetal Neonatal Med. 12 (3), 154–159.
Manjunatha, N., 2010. The current swine flu pandemic may provide some opportunity for future research of schizophrenia. Indian J. Med. Res. 132, 108–109.
McCarthy, M., Auger, D., Whittemore, S.R., 2000. Human cytomegalovirus causes productive infection and neuronal injury in differentiating fetal human central nervous system neuroepithelial precursor cells. J. Hum. Virol. 3 (4), 215–228.
McGuffin, P., Owen, M.J., Farmer, A.E., 1995. Genetic basis of schizophrenia. Lancet 346 (8976), 678–682.
Mednick, S.A., Machon, R.A., Huttunen, M.O., Bonett, D., 1988. Adult schizophrenia following prenatal exposure to an influenza epidemic. Arch. Gen. Psychiatry 45 (2), 189–192.
Moises, H.W., Ruger, R., Reynolds, G.P., Fleckenstein, B., 1988. Human Cytomegalovirus DNA in the temporal cortex of a schizophrenic patient. Eur. Arch. Psychiatry Neurol. Sci. 238 (2), 110–113.
Moore, T.H., Zammit, S., Lingford-Hughes, A., Barnes, T.R., Jones, P.B., Burke, M., et al., 2007. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 370 (9584), 319–328.
Mortensen, P.B., Norgaard-Pedersen, B., Waltoft, B.L., Sorensen, T.L., Hougaard, D., Torrey, E.F., et al., 2007. *Toxoplasma gondii* as a risk factor for early-onset schizophrenia: analysis of filter paper blood samples obtained at birth. Biol. Psychiatry 61 (5), 688–693.
Mortensen, P.B., Pedersen, C.B., Hougaard, D.M., Nørgaard-Petersen, B., Mors, O., Børglum, A.D., et al., 2010. A Danish National Birth Cohort study of maternal HSV-2 antibodies as a risk factor for schizophrenia in their offspring. Schizophr. Res. 122 (1–3), 257–263.

Na, K.S., Tae, S.H., Song, J.W., Kim, Y.K., 2009. Failure to detect Borna Disease Virus antibody and RNA from peripheral blood mononuclear cells of psychiatric patients. Psychiatry Investig. 6 (4), 306–312.
Nakamura, Y., Takahashi, H., Shoya, Y., Nakaya, T., Watanabe, M., Tomonaga, K., et al., 2000. Isolation of Borna Disease Virus from human brain tissue. J. Virol. 74 (10), 4601–4611.
Niebuhr, D.W., Millikan, A.M., Cowan, D.N., Yolken, R., Li, Y., Weber, N.S., 2008. Selected infectious agents and risk of schizophrenia among U.S. military personnel. Am. J. Psychiatry 165 (1), 99–106.
Nunes, S.O., Itano, E.N., Amarante, M.K., Reiche, E.M., Miranda, H.C., de Oliveira, C.E., et al., 2008. RNA from Borna Disease Virus in patients with schizophrenia, schizoaffective patients, and in their biological relatives. J. Clin. Lab. Anal. 22 (4), 314–320.
Otowa, T., Tochigi, M., Rogers, M., Umekage, T., Kato, N., Sasaki, T., 2006. Insertional polymorphism of Endogenous Retrovirus HERV-K115 in schizophrenia. Neurosci. Lett. 408 (3), 226–229.
Perron, H., Mekaoui, L., Bernard, C., Veas, F., Stefas, I., Leboyer, M., 2008. Endogenous Retrovirus type W GAG and envelope protein antigenemia in serum of schizophrenic patients. Biol. Psychiatry 64 (12), 1019–1023.
Prasad, K.M., Shirts, B.H., Yolken, R.H., Keshavan, M.S., Nimgaonkar, V.L., 2007. Brain morphological changes associated with exposure to HSV1 in first-episode schizophrenia. Mol. Psychiatry 12 (1), 105–113.
Riaza Gómez, M., de la Torre Espí, M., Mencía Bartolomé, S., Molina Cabañero, J.C., Tamariz-Martel Moreno, A., 1999. Complications of varicella in children. An. Esp. Pediatr. 50, 259–262.
Richt, J.A., Alexander, R.C., Herzog, S., Hooper, D.C., Kean, R., Spitsin, S., et al., 1997. Failure to detect Borna Disease Virus infection in peripheral blood leukocytes from humans with psychiatric disorders. J. Neurovirol. 3 (2), 174–178.
Rimon, R., Ahokas, A., Palo, J., 1986. Serum and cerebrospinal fluid antibodies to cytomegalovirus in schizophrenia. Acta Psychiatr. Scand. 73 (6), 642–644.
Robert-Guroff, M., Torrey, E.F., Brown, M., 1985. Retroviruses and schizophrenia. Br. J. Psychiatry 146, 326.
Rodgers-Johnson, P.E., Hickling, F.W., Irons, A., Johnson, B.K., Irons-Morgan, M., Stone, G.A., et al., 1996. Retroviruses and schizophrenia in Jamaica. Mol. Chem. Neuropathol. 28 (1–3), 237–243.
Scholbach, T., Bode, L., 2008. Borna Disease Virus infection in young children. APMIS Suppl. 124, 83–88.
Schwarcz, R., Hunter, C.A., 2007. *Toxoplasma gondii* and schizophrenia: linkage through astrocyte-derived kynurenic acid? Schizophr. Bull. 33 (3), 652–653.
Selten, J.P., Brown, A.S., Moons, K.G., Slaets, J.P., Susser, E.S., Kahn, R.S., 1999. Prenatal exposure to the 1957 influenza pandemic and non-affective psychosis in The Netherlands. Schizophr. Res. 38 (2–3), 85–91.
Selten, J.P., van Vliet, K., Pleyte, W., Herzog, S., Hoek, H.W., van Loon, A.M., 2000. Borna Disease Virus and schizophrenia in Surinamese immigrants to the Netherlands. Med. Microbiol. Immunol. 189 (2), 55–57.
Sham, P.C., O'Callaghan, E., Takei, N., Murray, G.K., Hare, E.H., Murray, R.M., 1992. Schizophrenia following pre-natal exposure to influenza epidemics between 1939 and 1960. Br. J. Psychiatry 160, 461–466.
Shrikhande, S., Hirsch, S.R., Coleman, J.C., Reveley, M.A., Dayton, R., 1985. Cytomegalovirus and schizophrenia. A test of a viral hypothesis. Br. J. Psychiatry 146, 503–506.
Sierra-Honigmann, A.M., Carbone, K.M., Yolken, R.H., 1995. Polymerase chain reaction (PCR) search for viral nucleic acid sequences in schizophrenia. Br. J. Psychiatry 166 (1), 55–60.
Smith, C.K., Arvin, A.M., 2009. Varicella in the fetus and newborn. Semin. Fetal Neonatal Med. 14 (4), 209–217.
Stevens, J.R., Langloss, J.M., Albrecht, P., Yolken, R., Wang, Y.N., 1984. A search for Cytomegalovirus and herpes viral antigen in brains of schizophrenic patients. Arch. Gen. Psychiatry 41 (8), 795–801.
Sullivan, P.F., Kendler, K.S., Neale, M.C., 2003. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch. Gen. Psychiatry 60 (12), 1187–1192.
Taller, A.M., Asher, D.M., Pomeroy, K.L., Eldadah, B.A., Godec, M.S., Falkai, P.G., et al., 1996. Search for viral nucleic acid sequences in brain tissues of patients with schizophrenia using nested polymerase chain reaction. Arch. Gen. Psychiatry 53 (1), 32–40.
Tamer, G.S., Dundar, D., Yalug, I., Caliskan, S., Yazar, S., Aker, A., 2008. The schizophrenia and *Toxoplasma gondii* connection: infectious, immune or both? Adv. Ther. 25 (7), 703–709.
Tandon, R., Keshavan, M.S., Nasrallah, H.A., 2008. Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. Schizophr. Res. 102 (1–3), 1–18.
Taylor, G.R., Crow, T.J., 1986. Viruses in human brains: a search for Cytomegalovirus and Herpes Virus 1 DNA in necropsy tissue from normal and neuropsychiatric cases. Psychol. Med. 16 (2), 289–295.
Terayama, H., Nishino, Y., Kishi, M., Ikuta, K., Itoh, M., Iwahashi, K., 2003. Detection of anti-Borna Disease Virus (BDV) antibodies from patients with schizophrenia and mood disorders in Japan. Psychiatry Res. 120 (2), 201–206.
Toro, C., Soriano, V., Grupo Español de Estudio del VIH-2 y HTLV-1/2, 2005. Current status of HIV-2 and HTLV-1/2 infection in Spain: lights and shades. Med. Clin. (Barc) 124 (16), 616–617.
Torrey, E.F., Yolken, R.H., Winfrey, C.J., 1982. Cytomegalovirus antibody in cerebrospinal fluid of schizophrenic patients detected by enzyme immunoassay. Science 216 (4548), 892–894.
Torrey, E.F., Bartko, J.J., Lun, R.Z., Yolken, R.H., 2007. Antibodies to *Toxoplasma gondii* in patients with schizophrenia: a meta-analysis. Schizophr. Bull. 33 (3), 729–736.
Tsuang, M., 2000. Schizophrenia: genes and environment. Biol. Psychiatry 47 (3), 210–220.
Voisset, C., Weiss, R.A., Griffiths, D.J., 2008. Human RNA "rumor" viruses: the search for novel human retroviruses in chronic disease. Microbiol. Mol. Biol. Rev. 72 (1), 157–196.
Waltrip, R.W., Buchanan, R.W., Summerfelt, A., Breier, A., Carpenter Jr., W.T., Bryant, N.L., et al., 1995. Borna Disease Virus and schizophrenia. Psychiatry Res. 56 (1), 33–44.
Yamaguchi, K., Sawada, T., Naraki, T., Igata-Yi, R., Shiraki, H., Horii, Y., et al., 1999. Detection of Borna Disease Virus-reactive antibodies from patients with psychiatric disorders and from horses by electrochemiluminescence immunoassay. Clin. Diagn. Lab. Immunol. 6 (5), 696–700.
Yolken, R.H., Bachmann, S., Ruslanova, I., Lillehoj, E., Ford, G., Torrey, E.F., et al., 2001. Antibodies to *Toxoplasma gondii* in individuals with first-episode schizophrenia. Clin. Infect. Dis. 32 (5), 842–844.
Yolken, R.H., Dickerson, F.B., Torrey, E.F., 2009. Toxoplasma and schizophrenia. Parasite Immunol. 31 (11), 706–715.
Ziebold, C., von Kries, R., Lang, R., Weigl, J., Schmitt, H.J., 2001. Severe complications of varicella in previously healthy children in Germany: a 1-year survey. Pediatrics 108 (5), E79.