

The Infection Hypothesis of Schizophrenia: A Systematic Review

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Abstract

Objectives: The objective of this paper is to accomplish a systematic review of the infection hypothesis of schizophrenia. **Methods:** All English language publications from January 1989 to March 2010 as related to infection and schizophrenia were obtained. Each study selected for analysis must either deal with the direct infection of an individual and schizophrenia or maternal infection during pregnancy and the subsequent development of schizophrenia in the offspring. The primary outcome measure was the calculated odds ratio and 95% confidence interval (CI). **Results:** Over 300 titles and abstracts were reviewed. Eight retrospective studies regarding in utero exposure were analyzed. Five nested case-controlled studies yielded an overall odds ratio of 3.58 (95% CI: 2.71 - 4.71) with a percent attributable risk of 6.3%. Three Scandinavian population studies yielded an overall odds ratio of 0.62 (95% CI: 0.49 - 0.79). Twenty-six papers were identified as retrospective studies focused on linking evidence of past infection in individuals with history of schizophrenia. A total of 77 microorganisms were assessed with 18 (23.4%) showing a positive association with schizophrenia. But positive associations in a given trial were negative in other trials. **Conclusions:** Direct infection of an individual as a cause of schizophrenia is unlikely. Results were mixed regarding maternal infection, in utero exposure, and the later development of schizophrenia in the offspring and likely accounts for a modest proportion of those with schizophrenia, possibly 6%.

Keywords: Infection Hypothesis, Schizophrenia

1. Introduction

The idea that a microorganism may be involved in the pathophysiology of mental illness is not new. An editorial contained in an 1896 issue of *Scientific American* suggested that certain kinds of mental illness might be due to infection (*Scientific American* 1896; 75: 303). In 1908, Chicago surgeon Bayard Taylor Holmes, believing that focal infections, perhaps in the gastrointestinal tract, induces a state of autointoxication that in turn causes mental and physical illness, wrote, "It is my opinion that there are many cases of insanity which are due to exogenous toxemia that should be sought for in the infection of some of the natural cavities of the body..." [1,2]. The neurodevelopmental model of schizophrenia proposes that schizophrenia is the ultimate result of a perturbation in brain development that occurs long before the manifestation of frank symptoms and that schizophrenia is caused by a complex combination of genetic

and environmental factors that are still poorly understood [3,4]. It is possible that a two-step mechanism involving (1) an internal genetic milieu that is permissive towards schizophrenia along with an (2) external environmental element(s) together provide the initial insult to neurodevelopment that pushes the individual to develop schizophrenia later in life. The environmental element in some instances could be infection.

Since the first part of the 20th century, largely following advances in molecular biology methods, mental health researchers have attempted to identify microorganisms that might be involved in the pathophysiology of mental illness, specifically schizophrenia. Many microorganisms have been implicated (**Table 1**) including viruses, bacteria, and at least one protozoan [5-7]. This paper identifies, reviews, analyzes, and quantifies the research on the infection hypothesis of schizophrenia. A systematic review was performed. The results and conclusions are discussed in the framework of the neuro-

Table 1. The infection hypothesis of schizophrenia - candidate microorganisms.

Viruses	Bacteria	Protozoan
Adenovirus 7	<i>Borrelia burgdorferi</i>	<i>Toxoplasma gondii</i>
Borna Disease Virus (BDV)	<i>Chlamydia trachomatis</i>	
Bovine Viral Diarrhea Virus (BVDV)	<i>Mycoplasma pneumoniae</i>	
Japanese Encephalitis Virus (JEV)		
Cytomegalovirus (CMV)		
Epstein-Barr Virus (EBV)		
Herpes Simplex Virus-1 (HSV-1)		
Herpes Simplex Virus-2 (HSV-2)		
Human Herpes Virus-6 (HHV-6)		
Varicella-Zoster Virus (VZV)		
Influenza Virus		
Measles Virus (Rubeola)		
Mumps Virus		
Human Parvovirus B19		
Coxsackie Virus B5		
Poliovirus		
Reovirus		
Human Immunodeficiency Virus (HIV)		
Rubella Virus		

developmental model of schizophrenia.

2. Methods

2.1. Search Strategy

All publications relevant to infection as it relates to schizophrenia were obtained according to standard guidelines [8]. The systematic review of the literature was restricted to English language sources from January 1989 to March 2010. The bottom limit of January 1989 was chosen because it coincided with the introduction and wide spread use of high quality polymerase chain reaction (PCR) technique that could reliably detect picomolar amounts of microorganism nucleic acid [9]. Electronic databases used were Cochrane Library, Medline, and PsycINFO. These online searches were augmented by hand reviewing the reference lists of identified papers. All available studies, reviews, and reports that mentioned some aspect of infection as it relates to schizophrenia were considered. Any microorganism mentioned as possibly being involved as causing schizophrenia was cataloged and listed in **Table 1**.

The Cochrane Library search used the keyword "schizophrenia." A primary search of Medline and PsycINFO used the keyword pairing of "schizophrenia" and "infection." A secondary search of Medline and Psy-

cINFO was done pairing the keyword "schizophrenia" with the specific microorganisms in **Table 1**.

2.2. The Definition of Schizophrenia

For the purpose of this review, the diagnosis of schizophrenia as defined by the authors of each study selected for analysis was accepted.

2.3. Selection Criteria and Primary Outcome Measure

In order to be included for analysis in this review, each study must satisfy the following two selection factors:

- 1) Focus of a selected study must be either on the direct infection of an individual and schizophrenia or maternal infection during pregnancy with subsequent development of schizophrenia in the offspring.
- 2) Each selected study must contain sufficient data to calculate an odds ratio.

The primary outcome measure is the calculated odds ratio along with the 95% confidence interval. The odds ratio was chosen because it is a statistic that estimates the relative risk in case-controlled studies[10], which was the study design anticipated to be encountered most frequently. The odds ratio and 95% confidence interval (CI) were calculated according to the method described by

Dawson and Trapp [10]. Studies yielding positive or negative results were included. Case reports and reviews were used to augment the search process, but not used for analysis. The search was not limited to any one specific microorganism.

2.4. Addressing Missing Data

For those studies that lent themselves to yielding an odds ratio, but data within the paper were either incomplete or absent, the principal investigator was contacted and asked for those appropriate data in order to calculate odds ratios.

2.5. Data Extraction and Analysis

Data from each study, review, and report were recorded on a data extraction form. Information abstracted included microorganism(s), study design, details regarding method, and results. Studies eligible for analysis were used to calculate an odds ratio. Homogeneity among studies was determined by the results of graphically plotting the proportion of those with schizophrenia onset in the infection-exposed groups on the vertical axis and the proportion of those with schizophrenia onset in the control groups on the horizontal axis. A linear trend was assumed to indicate good homogeneity. Where appropri-

ate, numbers were combined to generate an overall odds ratio and 95% confidence interval. Where appropriate, the percent attributable risk, the percent of occurrence of the disorder in those individuals exposed that is due to the exposure, was then calculated [11].

3. Results

Over 300 titles and abstracts were reviewed. No prospective cohort studies were found with the specific aim of following into adulthood the children of mothers with documented infection during pregnancy and assessing psychiatric status. No studies were found demonstrating the development of schizophrenia in an individual subsequent to an episode of infection.

With respect to indirect evidence linking infection and schizophrenia, 13 papers were initially identified as being retrospective cohort studies focusing on maternal infection during pregnancy and the later development of schizophrenia in adult offspring [12-24]. All but two [17, 20] reported a positive association between infection and the development of schizophrenia in the adult offspring. Five studies were excluded because of missing data [12,15,19,21,23]. The analysis for the remaining eight studies is displayed in **Table 2**. A graphical assessment (**Figure 1**) revealed reasonable homogeneity amongst the first five nested case controlled studies. Thus those data

Table 2. Maternal infection, in utero exposure, and later development of schizophrenia in the offspring.

Study	Microorganism or Medical Condition Related to Infection	Basis for Infection Diagnosis During Pregnancy	Number with Schizophrenia and Exposure	Number without Schizophrenia and Exposure	Number with Schizophrenia and No Exposure	Number without Schizophrenia and No Exposure	Odds Ratio	95% Confidence Interval
Brown <i>et al.</i> , 2006 [17]	HSV-1/HSV-2	Serologically	16	24	55	86	1.04	0.48 - 2.26
Brown <i>et al.</i> , 2005 [16]	<i>Toxoplasma gondii</i>	Serologically	18	22	45	101	1.84	0.85 - 3.98
Brown <i>et al.</i> , 2004 [13]	Influenza virus	Serologically	22	37	85	163	1.14	0.61 - 2.14
Brown <i>et al.</i> , 2000 [18]	Respiratory infections	Clinically	9	623	49	7,100	2.09	0.96 - 4.44
Brown <i>et al.</i> , 2000 [14]	Rubella virus	Clinically	11	59	15*	1,511	18.78	7.67 - 45.66
Clarke <i>et al.</i> , 2009 [20]	Pyelonephritis	Finnish Medical Registry	36	9,560	35	13,773	1.48	0.908 - 2.419
Mortensen <i>et al.</i> , 2007 [22]	<i>Toxoplasma gondii</i>	Danish Medical Registry & Biobank	17	68	54	616	2.85	1.50 - 5.39
Sorensen <i>et al.</i> , 2009 [24]	Bacterial Infection	Copenhagen Perinatal Cohort	38	1,027	200	6,675	1.24	0.85 - 1.78
Combining First Five Studies			76	765	249	8,961	3.58	2.71 - 4.71
Combining Population Studies			91	10,655	289	21,064	0.62	0.49 - 0.79

* The number with schizophrenia and with no in utero exposure was estimated. Assuming a 1% prevalence of schizophrenia, then $1,511 \times 0.01 \approx 15$.

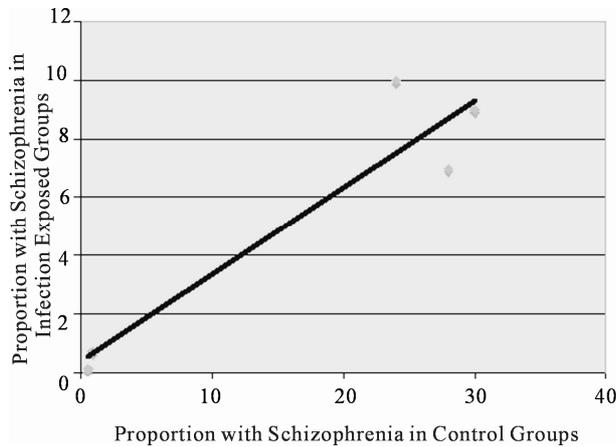


Figure 1. Heterogeneity determination.

from the first five studies were pooled. The overall odds ratio from the first five studies showed an increased likelihood of schizophrenia among those exposed to maternal infection while in utero (Overall Odds Ratio = 3.58; 95% CI: 2.71 - 4.71) with a percent attributable risk of 6.3%. Given the use of Scandinavian national databases, the population studies were assumed to be homogeneous and were combined. The three population studies yielded an overall odds ratio that suggested no increased likelihood of schizophrenia among those exposed to maternal infection while in utero (Overall Odds Ratio = 0.62; 95% CI: 0.49 - 0.79).

Another 26 published retrospective cohort studies attempted to link evidence of past infection with schizophrenia [25-50] (*i.e.*, direct exposure to infection). Sam-

ples ranged from post-mortem brain tissue to blood from patients and controls. Standard molecular biology techniques were used such as enzyme linked immunosorbent assay (ELISA), Western blot, and polymerase chain reaction (PCR). Frequently, multiple microorganisms were assessed in a given study. Taking each microorganism investigated as a separate trial, 23.4% of trials yielded a positive association (18 out of 77 trials; **Table 3**).

The 18 separate trials were published in 16 papers [27, 28,31,32,34-39,41-43,47,49,50]. Five trials from four papers were excluded because of missing data [27,36, 39,42]. Two positive trials focusing on other issues instead of infection causing schizophrenia were also excluded [31,32]. Eleven trials were included in the analysis (**Table 4**). A graphical assessment (**Figure 2**) revealed poor homogeneity amongst these 11 trials. Thus individual odds ratios were calculated for each of the 11 eligible trials and presented in **Table 4**. No overall odds ratio was calculated because homogeneity could not be assumed. One of those 11 trials contained zero in the odds ratio calculation [35], but still was listed in **Table 4**. Two separate studies seemed to use identical data [36,37].

Five studies were found that specifically investigated CNS infection occurring during childhood and the later development of schizophrenia [51-55]. Although all five studies showed a positive association between childhood CNS infection and the later development of schizophrenia, the possibility of infection-induced brain damage resulting in schizophrenia-like psychiatric symptoms could not be ruled out. Thus, these studies were not included for analysis.

Table 3. Evidence of past infection and history of schizophrenia - microorganisms investigated and outcome (77 total trials).

Microorganism	Number of Positive Associations with Schizophrenia	Number of Negative Associations with Schizophrenia
Borna Disease Virus (BDV)	7 (9.1%)	3 (3.9%)
Bovine Viral Diarrhea Virus (BVDV)	0	1 (1.3%)
Japanese Encephalitis Virus (JEV)	0	1 (1.3%)
Cytomegalovirus (CMV)	2 (2.6%)	8 (10.4%)
Epstein-Barr Virus (EBV)	0	8 (10.4%)
Herpes Simplex Virus-1 (HSV-1)	1 (1.3%)	6 (7.8%)
Herpes Simplex Virus-2 (HSV-2)	0	5 (6.5%)
Human Herpes Virus-6 (HHV-6)	1 (1.3%)	6 (7.8%)
Varicella-Zoster Virus (VZV)	0	8 (10.4%)
Influenza Virus	0	5 (6.5%)
Measles Virus (Rubeola)	0	2 (2.6%)
Mumps Virus	0	2 (2.6%)
Retrovirus	2 (2.6%)	1 (1.3%)
Human Immunodeficiency Virus (HIV)	0	1 (1.3%)
Rubella Virus	0	1 (1.3%)
<i>Toxoplasma gondii</i>	5 (6.5%)	1 (1.3%)
Totals	18 (23.4%)	59 (76.6%)

Table 4. History of direct infection in individuals and the development of schizophrenia*.

Study	Microorganism	Number with Schizophrenia and Exposure	Number without Schizophrenia and Exposure	Number with Schizophrenia and No Exposure	Number without Schizophrenia and No Exposure	Odds Ratio	95% Confidence Interval
Nunes <i>et al.</i> , 2008 [43]	BDV	12	4	15	23	4.60	1.08 - 21.09
Chen <i>et al.</i> , 1999 [28]	BDV	38	32	276	459	1.97	1.17 - 3.33
Iwahashi <i>et al.</i> , 1998 [37]	BDV	30	1	37	30	24.32	3.21 - 513.30
Iwahashi <i>et al.</i> , 1998 [36]	BDV	30	1	37	30	24.32	3.21 - 513.30
Iwahashi <i>et al.</i> , 1997 [35]	BDV	30	0	37	26	NA	NA
Waltrip II <i>et al.</i> , 1995 [49]	BDV	15	3	75	17	1.13	0.26 - 5.55
Hart <i>et al.</i> , 1999 [34]	Retrovirus	29	4	38	12	2.29	0.60 - 9.46
Lillehoj <i>et al.</i> , 2000 [40]	Retrovirus	11	1	27	26	10.60	1.24 - 238.79
Niebuhr <i>et al.</i> , 2008 [41]	<i>Toxoplasma gondii</i>	15	37	165	491	1.21	0.62 - 2.34
Tamer <i>et al.</i> , 2008 [47]	<i>Toxoplasma gondii</i>	16	6	24	31	3.44	1.05 - 11.73
Yolken <i>et al.</i> , 2001 [50]	<i>Toxoplasma gondii</i>	14	3	24	24	4.67	1.05 - 23.04

* BDV = Borna Disease Virus, NA = Not Applicable.

4. Discussion

Edwin Goodall, a President of the Section of Psychiatry in the British Royal Society of Medicine, lecturing in

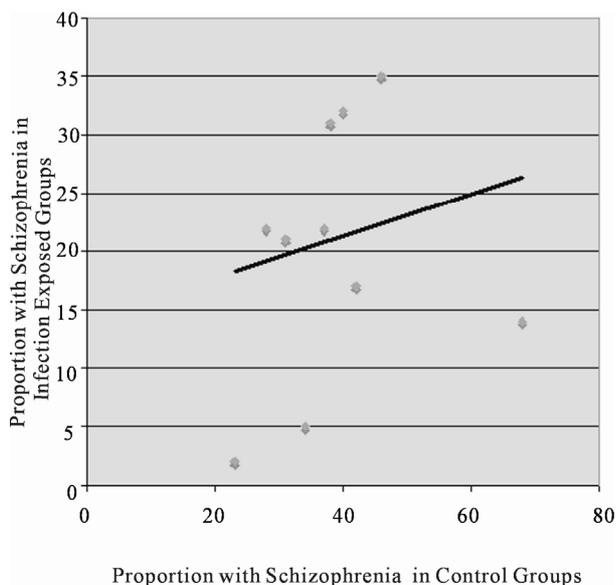


Figure 2. Heterogeneity determination.

1932, stated, "...there is no essential difference connected with encephalitis (post-encephalitic) and those met within states covered by the description schizophrenia" [56]. Goodall went on to speculate, "...that a virus or toxin is the causative factor...vaccina, varicella, variola, measles, perhaps influenza." Following Goodall's lead, it was later observed that there appears to be a 5% to 8% excess of late winter and early spring births of individuals who later in life develop schizophrenia [57]. This season-of-birth effect implied that maternal infection during pregnancy might be a factor in causing schizophrenia in the offspring. Further, data extrapolated from the analysis of ecological events, mostly the influenza pandemics, have linked prenatal exposures to infectious agents to the risk of developing schizophrenia later in life [58-69], although not all of those ecological studies showed a positive association [70-75]. In a review of prenatal infection and schizophrenia published in March 2010 Brown and Derkits [76] contend that of those individuals with schizophrenia perhaps as many as 30% could have been prevented if certain infections could have been avoided among pregnant women. The idea that infection is involved in the pathophysiology of schizophrenia simply will not go away.

Although direct infection of an individual can produce psychiatric symptoms that look like schizophrenia [77,78], three findings in this review argue against direct infection and the subsequent development of schizophrenia. First, as indicated in **Table 3**, there was essentially no consistency across studies as 76.6% of the possible associations were negative. Further, those microorganisms that produced positive associations in some trials also produced negative associations in other trials. Second, appropriate temporal sequencing was a concern because it was unclear precisely when infection occurred with respect to the onset of schizophrenia. It is known that about 75% of those individuals with schizophrenia also have a co-occurring physical health problem such as heart disease, cancer, or diabetes [79]. It then would not be unusual to find evidence of past infection by a variety of microorganisms in this population. Third, of those studies in which an odds ratio could be derived (**Table 4**), three contained one in the 95% confidence interval calculation. Another three had exceedingly wide confidence intervals. These statistical results call into question whether a true association actually exists. Finally, it is more biologically plausible that schizophrenia is a neurodevelopmental disorder and not the sequela of acute infection. An infection process that precipitates psychotic symptoms is better characterized as delirium or psychosis due to a medical condition as opposed to schizophrenia. Taken together, these findings suggest it is unlikely that direct infection of an individual is a cause of schizophrenia.

Table 2 shows mixed evidence regarding maternal infection during pregnancy and the later development of schizophrenia in the offspring. The first five studies are unique in that each study was a nested case controlled design that drew upon well-defined populations and each of the five studies were done by the same research group. Overall, the findings suggested a 3.58 (95% CI: 2.71 - 4.71) greater risk of later development of schizophrenia in offspring with in utero exposure to a microorganism, and/or the products and consequences of infection, than in those without such exposure. This in utero effect may account for up to 6% of cases of schizophrenia. These results stand in contrast to the three Scandinavian population studies that actually indicate a protective effect with respect to maternal infection with an overall odds ratio of 0.62 (95% CI: 0.49 - 0.79). If those data across all of the studies in **Table 2** were combined the odds ratio becomes 0.82 with a 95% confidence interval of 0.68 to 0.98; perilously close to one and implying that maternal infection is not a major cause of schizophrenia in the offspring.

Microorganisms and humans evolved together. It is no surprise that there exists many connections, overlaps, and

interactions between microorganisms and human physiological chemistry [80]. One might consider evoking the hygiene hypothesis [81] and say that a certain amount of maternal infection or microbial colonization is tolerated, perhaps even required, during pregnancy. But, it may be that once a critical inflection point is reached with respect to microbial involvement, fetal and/or maternal tolerances may be breached thus placing the developing fetal nervous system at some degree of risk. An explanation that fits with the neurodevelopmental model of schizophrenia is that microbial gene products that mimic host cytokines (such as virokines [82,83] or other pseudo-cytokines from bacteria or protozoans) and/or the generation of pro-inflammatory cytokines [84,85] may perturb fetal neurodevelopment in a subtle, but significant way that later results in the development of schizophrenia. At what neuro-location within the fetus and at what moment of development is most vulnerable are unknown, but stochastic factors are likely involved. Unfortunately, nothing was said about the fathers of those offspring who later went on to develop schizophrenia. There is reason to believe that older paternal age is a risk factor for the later development of schizophrenia in the offspring [86]. Paternal age then was a possible confounding factor in those studies focusing on maternal infection. Finally, none of the studies surveyed for this review could account for the lack of increase in prevalence of schizophrenia in those areas of the world where infectious disease is prominent [87]. There is evidence that schizophrenia is more prevalent in the developed countries where one would think that public health measures and infection control would be the best [88]. Thus, in utero exposure to a microorganism, and/or the products or consequences of infection, as a cause of schizophrenia - although a good example of gene/environment interaction [80,89] and consistent with the neurodevelopmental model of schizophrenia - may only account for a modest proportion of those individuals with schizophrenia, perhaps 6%.

This systematic review has several limitations. First, it only contained studies that were published after January 1989. Unpublished reports and studies in languages other than English were not collected. Thus not every study regarding infection and schizophrenia was evaluated in the formal analysis. Second, the problem of missing data was difficult to overcome. Therefore several studies needed to be excluded from formal analysis. Third, homogeneity was a major problem for those studies attempting to relate direct infection in an individual and the subsequent development of schizophrenia (**Table 4**). This precluded combining odds ratio data in any straightforward way. Fourth, the definition of schizophrenia varied from study to study. It frequently was

difficult to differentiate a valid diagnosis of schizophrenia from a medical condition manifesting with schizophrenia-like symptoms, such as delirium or psychosis due to a medical condition.

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