

*The Emerging Epidemiology of  
Hepatitis E Virus: The United  
States as a Case Study*

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## *Autochthonous Hepatitis E - US Reports*

Study	Year	Individual
Kwo et al.	1997	Caucasian Minnesota man
Tsang et al.	2000	Caucasian California man
Amon et al.	2006	Asian Texas woman
Curry et al.	2009	HIV + man

# Hepatitis E Virus – US Epidemiology

Study	Year	Assay	Population	N	Seroprevalence	Finding
Thomas et al.	1997	NIH/ Genelabs	Baltimore MSM	295	16%	Age trend
			Baltimore IDU	295	23%	Age trend
			Baltimore blood donors	300	21%	-
			Sacramento blood donors	211	14%	-
			New York blood donors	300	31%	-
Smith et al.	2002	NIH	Los Angeles homeless	200	14%	Age trend
Withers et al.	2002	WRAIR	North Carolina swine workers	165	11%	Foreign birth
			North Carolina residents	127	2%	-
Meng et al.	2002	NIH	US swine veterinarians	295	23%	Age trend
			US agricultural state blood donors	400	18%	Age trend

# Correlates of HEV, HBV and HAV in selected Populations

## A. MSMs

Factor	HEV	HBV	HAV
Age	+	+	+
Hx Hepatitis	0	++ (8.3)	++ (7.6)
RPR	0	++ (4.8)	0
HIV+	0	+ (2.5)	+ (1.6)

# Correlates of HEV, HBV and HAV in selected Populations

## B. IDUs

Factor	HEV	HAV
Age	0	+ (2.5)
Hx hepatitis	0	+ (1.6)
Duration IDU	0	++ (4.8)
Current IDU	0	++ (4.8)
Hx STD	0	0
No Sex partner	0	0

# **Epidemiology of Hepatitis E Virus in the United States: Results from NHANES III, 1988-1994**

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## *Two Key Questions*

1. Where does the substantial HEV seroprevalence in industrialized countries come from?
2. What is the origin of autochthonous hepatitis E in industrialized countries in persons who do not report any direct exposure to animal HEV reservoirs?



## *Methods Summary*

We tested a nationally representative sample of the US population for anti-HEV IgG antibodies using a highly sensitive and specific enzyme immunoassay. We documented overall and subgroup-specific HEV seroprevalence in the US and examined associations between HEV seropositivity and putative risk factors



## *Methods: Study Population*

- A cross-sectional study of the US civilian non-institutionalized population, 1988-94; hard-to-reach populations were oversampled
- Participants were interviewed, underwent a physical exam and provided blood samples
- Serum samples from 18,695 NHANES III study participants  $\geq 6$  years were available.

## *Methods: Lab Methods*

- Recombinant capsid protein containing the complete ORF-2 region (Tsarev SA et al. *J Infect Dis* 1993)
- Negative control serum from naïve chimpanzees
- Positive controls are serial dilutions of a model of the WHO 95/584 anti-HEV preparation

## *Methods: Lab Methods (cont.)*

- 109 putatively seropositive samples sent to NIAD/NIH for confirmation with blocking assay (Sar55)
- Final seropositivity cut-point translated to a mean of 0.016 WHO units (standard deviation: 0.0025 WHO units)
- 92% positive predictive value compared to the blocking assay conducted at NIAID



## *Methods: Statistical Methods*

- All statistical analyses were performed using specification of NHANES III design parameters as well as sample weights
- All lab testing was conducted in a blinded fashion; lab results were linked to the NHANES III data set only following the completion of all laboratory testing (i.e. non-differential misclassification)

## *Results: Prevalence of anti-HEV IgG*

Variable	N	% Positive (95% CI)
All subjects	18695	21 (19, 23)
Gender		
Female	10124	20 (18, 23)
Male	8571	22 (19, 24)
Race/Ethnicity		
White (reference)	7052	22 (20, 24)
Black	5312	15 (13, 16)*
Mexican-American	5527	20 (18, 22)
Other	804	20 (17, 24)

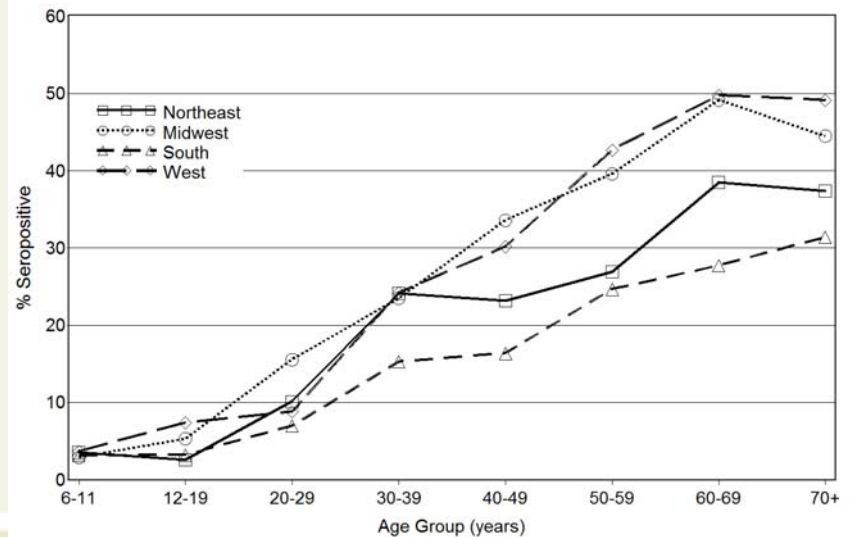
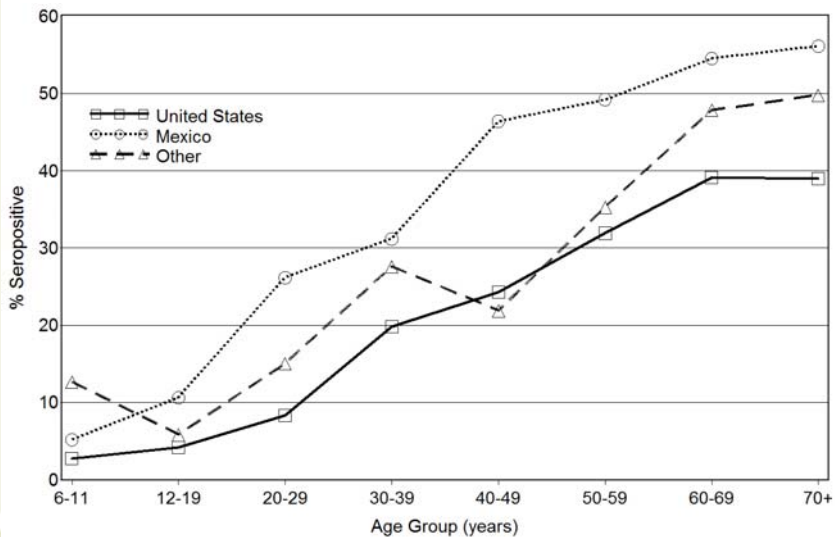
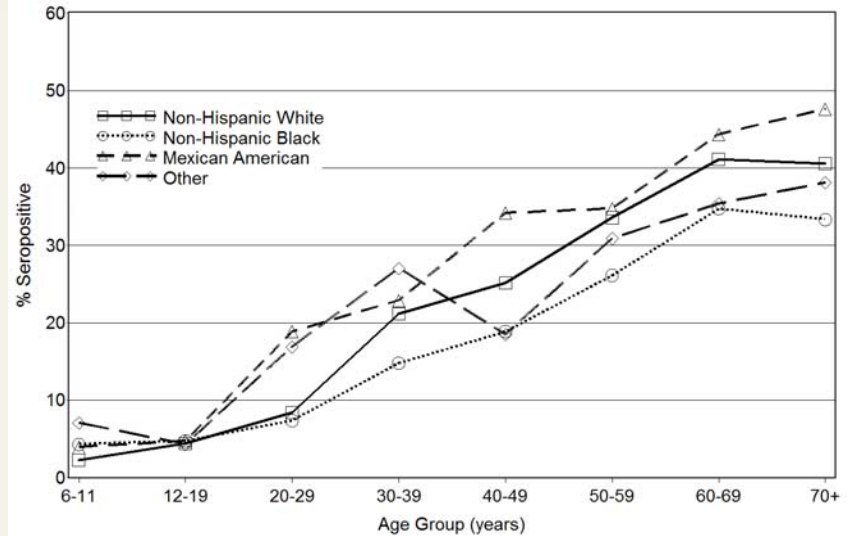
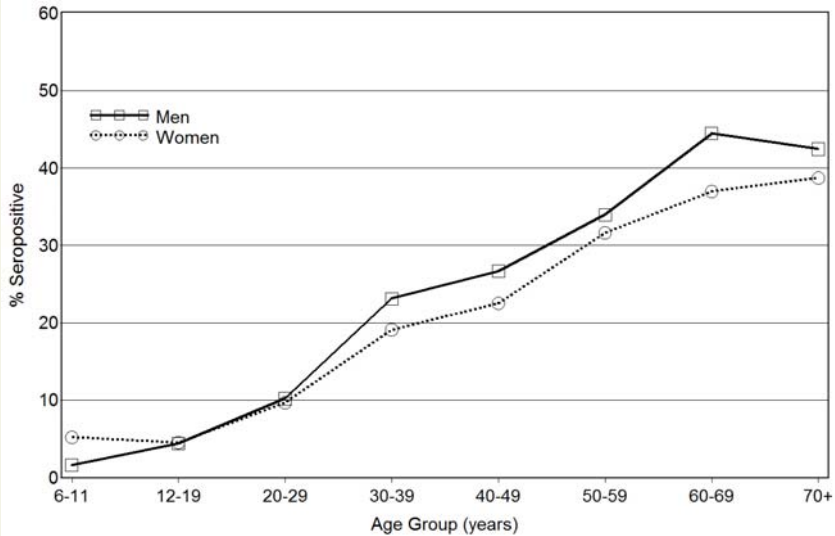
\*  $p < 0.05$  compared to reference group

## Results: Prevalence of anti-HEV IgG

Variable	N	% Positive (95% CI)
Country of birth		
US (reference)	15051	20 (18, 22)
Mexico	2357	31 (29, 33)*
Other	1233	26 (23, 30)*
Region of residence		
South (reference)	8168	15 (12, 17)
Northeast	2372	21 (17, 25)*
Midwest	3655	27 (22, 31)*
West	4500	25 (21, 29)*

\*  $p < 0.05$  compared to reference group

# Results: Prevalence of anti-HEV IgG



## Results: US born, age-adjusted

Variable	White		Black		Mexican-American	
	N	% Positive	N	% Positive	N	% Positive
Sex						
Female	3681	19	2783	16	1673	15
Male	3026	21	2199	17	1461	17
Region						
South (ref)	2669	14	2877	13	1463	14
Northeast	1107	19*	675	21*	15	¶
Midwest	1905	25*	1078	21*	260	22*
West	1026	25*	352	18*	1396	16

\*  $p < 0.05$  compared to reference group



## Results: US born, age-adjusted

Variable	White		Black		Mexican-American	
	N	% Positive	N	% Positive	N	% Positive
Persons/room						
< 0.8 (ref)	5828	20	3065	17	1546	17
0.8 – 1.2	783	22	1462	17	1042	12*
> 1.2	75	¶	444	15*	542	16
Residence						
Non-metro	4254	16	2388	13	1691	14
Metro	2453	25*	2594	19*	1443	18
Poverty						
≥ poverty line	6051	20	3349	16	2133	16
< poverty line	656	17	1633	16	1001	14

\* p < 0.05 compared to reference group

## Results: US born, Prevalence & ORs

Variable	N	% Positive	OR* (95% CI)
Military Service			
No	9922	21	1.0
Yes	1998	33	1.21 (0.99, 1.48)
Source of tap water			
Water company	11782	20	1.0
Well	1691	19	<b>0.78 (0.63, 0.97)</b>
Spring	40	19	0.64 (0.30, 1.37)
Number life sex partners			
1-10	5944	19	1.0
> 10	1604	19	0.91 (0.73, 1.14)

\* adjusted for age, sex, race/ethnicity, and region of residence

## Results: US born, Prevalence & ORs

Variable	N	% Positive	OR* (95% CI)
Ever male-to-male sex			
No	5034	24	1.0
Yes	258	23	1.09 (0.68, 1.74)
Ever cocaine or crack			
No	10968	24	1.0
Yes	998	17	0.95 (0.75, 1.21)
Any pet			
No	9589	20	1.0
Yes	5461	20	<b>1.19 (1.01, 1.40)</b>

\* adjusted for age, sex, race/ethnicity, and region of residence

## Results: US born, Prevalence & ORs

Variable	N	% Positive	OR* (95% CI)
Pet dog			
No	11616	20	1.0
Yes	3433	21	<b>1.22 (1.04, 1.43)</b>
Pet cat			
No	12709	20	1.0
Yes	2340	20	1.12 (0.90, 1.38)
Bacon/sausage/processed meats – times/month			
0 – 10	9581	22	1.0
11 - 20	1754	18	0.96 (0.75, 1.21)
> 20	1965	20	0.89 (0.65, 1.22)

\* adjusted for age, sex, race/ethnicity, and region of residence

## Results: US born, Prevalence & ORs

Variable	N	% Positive	OR* (95% CI)
Liver/other organ meats – times/month			
0	9875	20	1.0
1	1763	25	1.15 (0.96, 1.36)
> 1	1656	27	<b>1.38 (1.01, 1.88)</b>
Pork/ham – times/month			
0 – 5	10600	22	1.0
6 - 10	1710	18	0.98 (0.75, 1.27)
> 10	992	16	0.78 (0.60, 1.02)

\* adjusted for age, sex, race/ethnicity, and region of residence

## Results: US born, Prevalence & ORs

Variable	No.	% Positive	OR* (95% CI)
Anti-HCV			
Negative	14540	20	1.0
Positive	292	29	<b>1.71 (1.07, 2.74)</b>
Anti-HBc			
Negative	14020	20	1.0
Positive	845	29	1.37 (1.00, 1.86)
Anti-HAV			
Negative	9170	18	1.0
Positive	5693	26	<b>0.80 (0.70, 0.92)</b>

\* adjusted for age, sex, race/ethnicity, and region of residence

## *Why High Prevalence in '88 - '94?*

- Prevalence found in this study is similar to previous estimates with this assay
- This assay may detect remote infections better than commercial tests designed to diagnose hepatitis E
- This assay detects antibody to genotypes 1 and 3 equally well
- Exposure to HEV varies markedly by geographic region

## *Why is Hepatitis E rare in the US?*

- Exposure to genotype 3 viruses; may be less virulent than other genotypes
- HEV may cause clinical symptoms in a dose-dependent manner and US individuals may be exposed to only low doses of virus
- Autochthonous hepatitis E may be underreported in the US; there is no FDA licensed anti-HEV assay



## *Exposure in Developing Countries?*

- Significant association of anti-HEV with foreign birth
- Elevated OR for military service
- NHANES III did not assess foreign travel
- A substantial proportion of seroprevalence in this study likely stems from exposure to HEV in developing countries

## *Exposure to Pets and Organ Meats?*

- Anti-HEV is commonly found in many animals but HEV RNA is rarely detected from animals besides swine
- Pets may be dead end hosts
- Confounding may explain association between pets and anti-HEV
- The association with organ meats is consistent with previous studies

## *Other Routes of Exposure?*

- Association with anti-HCV and anti-HBc is consistent with a hypothesis of transfusion-transmitted infection
- Cocaine & crack use not associated with anti-HEV
- Extensive geographic and racial/ethnic heterogeneity suggest other mechanisms



# *Strengths and Limitations*

## Strengths

- Largest study of HEV epidemiology to date
- Includes children & elderly
- Extensive demographic and dietary info
- Collaboration with NIAID and CDC

## Limitations

- Lab testing not perfectly predictive; but non-differential
- Does not provide info on trends over time

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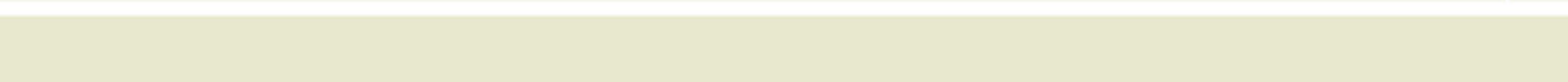
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*Thank You!*

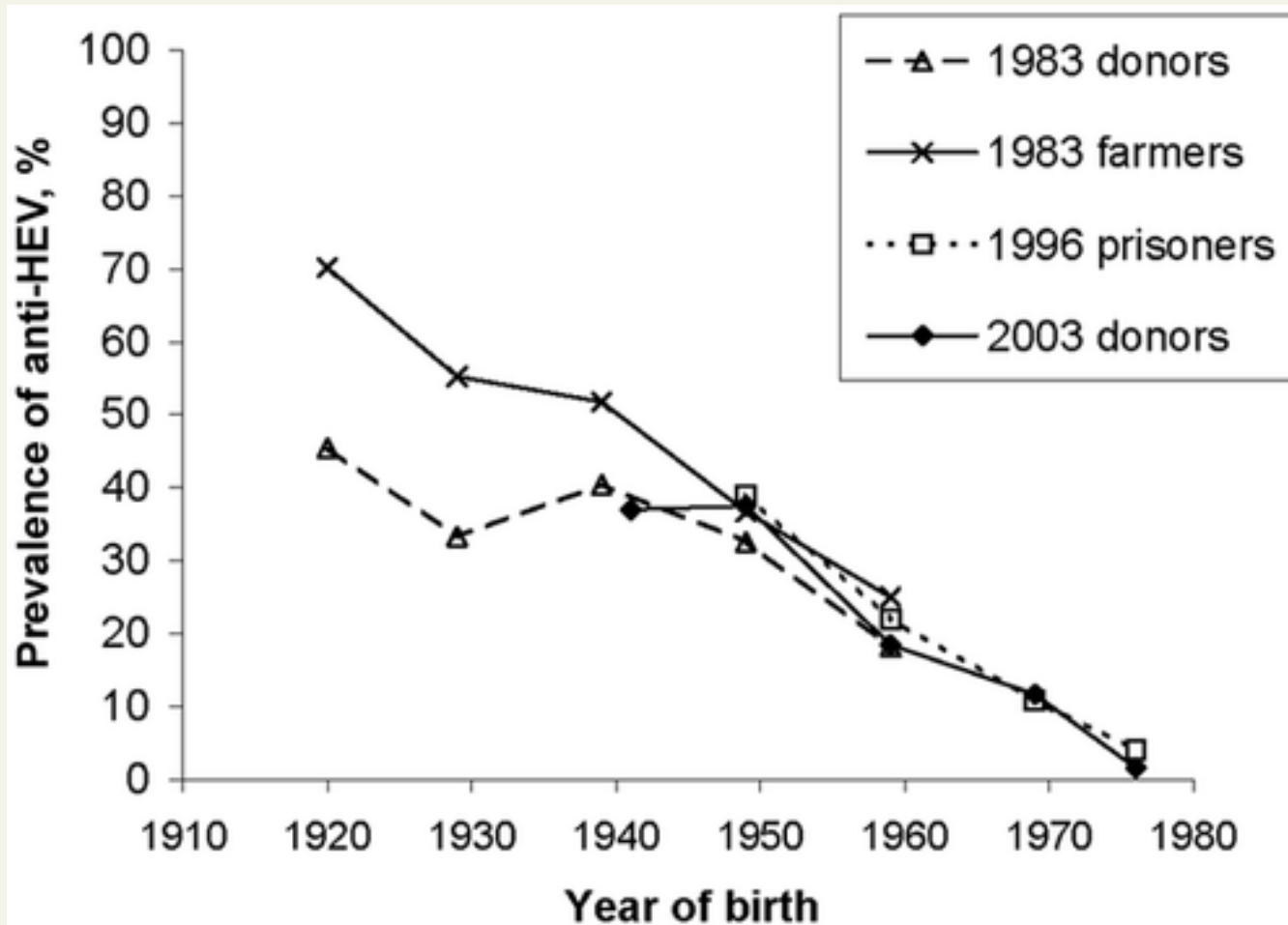




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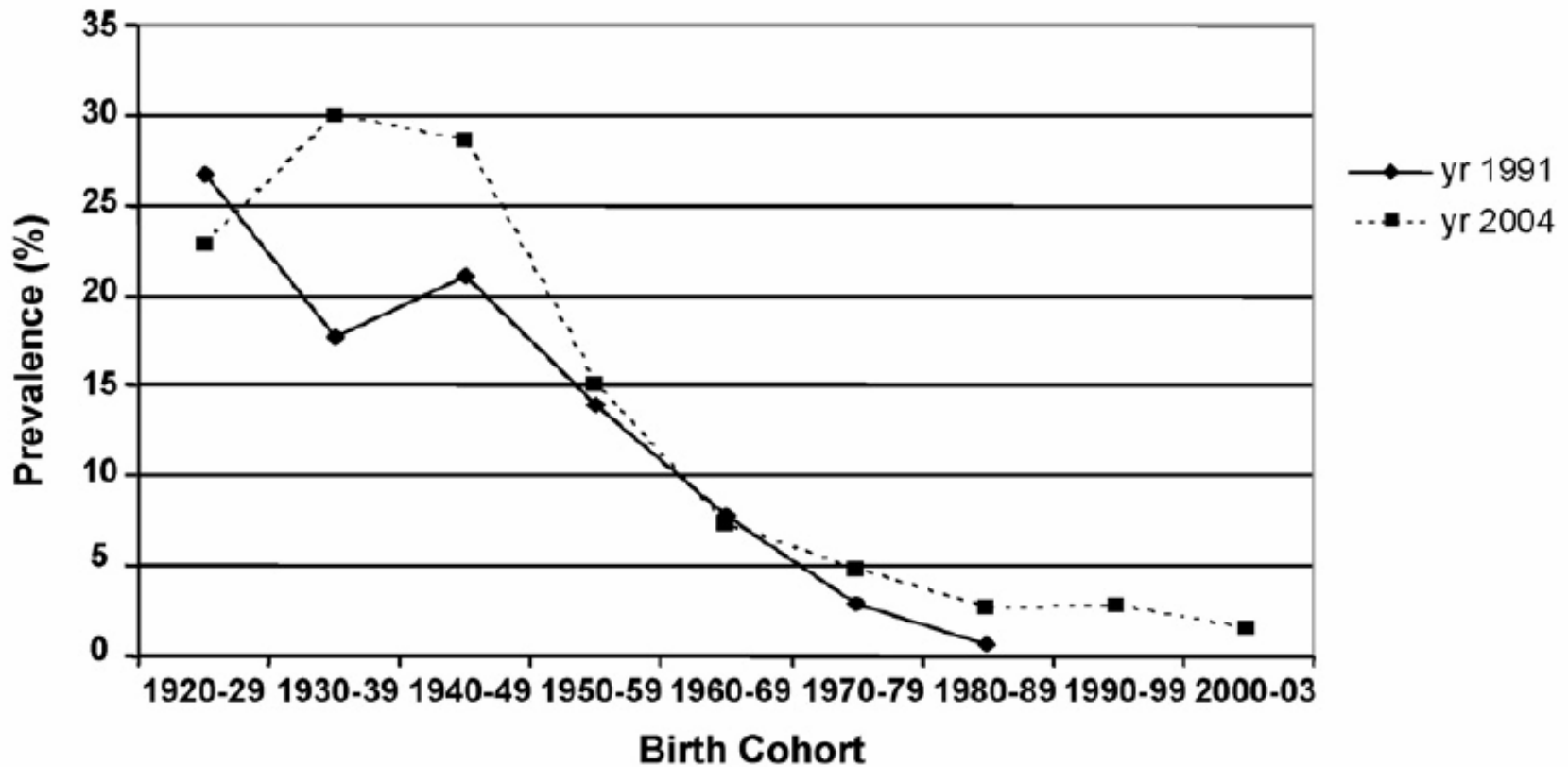


# Is Prevalence Declining? Denmark





# Is Prevalence Declining? England



# Continuing Transmission? England

