

HEP DART 2005

frontiers in drug development for viral hepatitis

Innovative Horizon Lecture
**Complex interactions of HBV
and its hosts: alterations of
human gender ratio**

Baruch Blumberg
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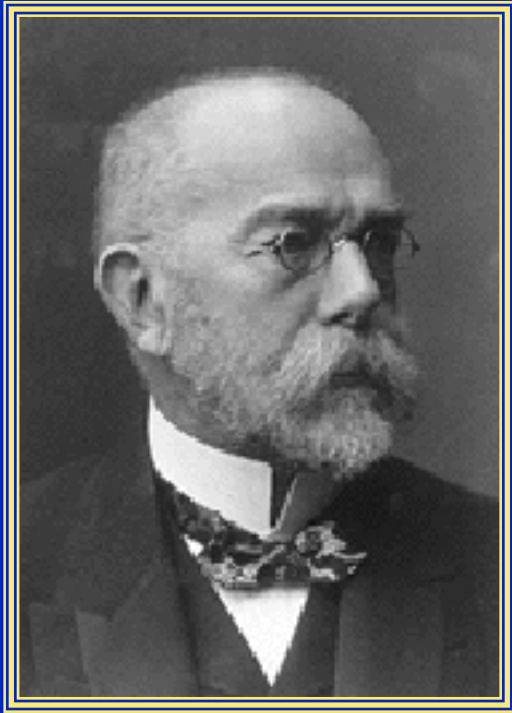
HEPDART 2005
Kohala Coast, Big Island, Hawaii
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**COMPLEX INTERACTIONS OF HBV
AND ITS HOSTS**
Alterations of human gender ratio

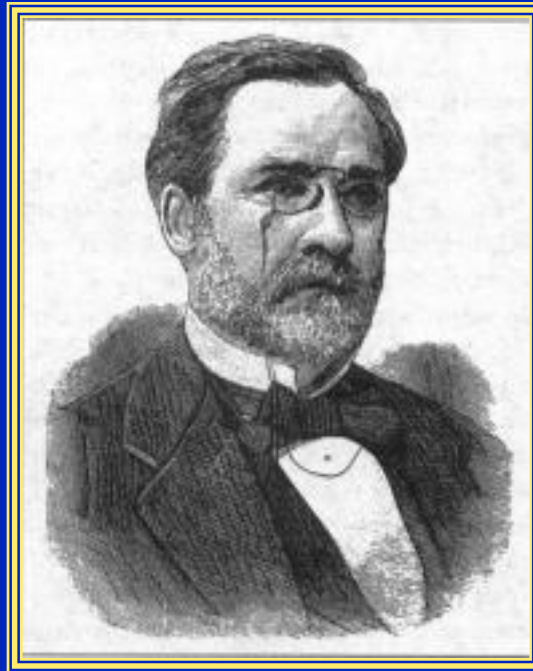
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OUTLINE

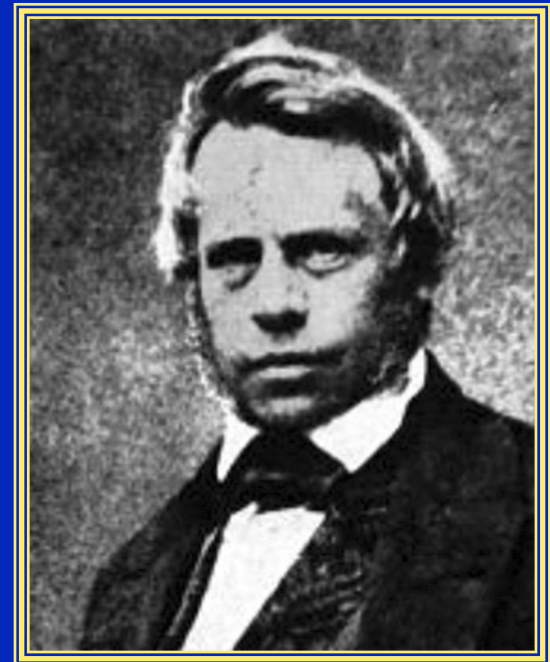
1. The germ theory of disease was one of the great advances in medical science. However it does not provide a satisfactory description of the interaction of microorganisms with their hosts and their environment.
2. HBV infects a large portion of the world's population and is deadly to many.
3. There is a complex series of genetic polymorphic loci that affect the host response to HBV infection. These loci also affect other microorganisms. (The Microorganisms Gene Affinity Cluster.)
4. Genetic polymorphisms have advantages and disadvantages. There are important non-pathological effects of HBV infection.
5. The vaccination program has greatly decreased the prevalence of HBV carriers and the incidence of HBV related hepatitis and primary cancer of the liver.
6. There are striking differences in the response of males and females to infection with HBV.
7. In family studies, parents who are carriers of HBV have a higher ratio of males to females in their offspring than parents who are not carriers.
8. Population studies confirm these observations and indicate that HBV has a major effect on gender ratio in many parts of the world.
9. The gender ratio effect has been significantly altered by the vaccination program. This will have profound demographic effect particularly in populations with a high prevalence of HBV infection and small family size.
10. HBV carriers retain more iron than non-carriers. This may be advantageous in the young but disadvantageous in the elderly.
11. There is a nuanced, complex and non-intuitive interplay of many factors that determine the overall effects of HBV in a population. It is important to understand these as the vaccination programs proceed.



Robert Koch



Louis Pasteur



Friedrich Henle

KOCH'S POSTULATES

- The suspected agent is associated with the disease in question. In some formulations it is found in *all* cases of the disease.
- The suspected agent is removed from the affected tissues of a patient with the disease and grown in pure culture outside the original host. Viruses require cells and tissues to grow in rather than a cell-free medium that can nourish bacteria.
- The isolated suspected agent is then transmitted to experimental animals.
- The infected animals develop the same disease as the patient.
- The suspected agent is then isolated from the infected animal and transmitted to a second experimental animal.
- The second animal develops the same disease as the patient.

COMMENTS ON KOCH'S POSTULATES

There is a focus on organisms that cause disease.

**The non-disease aspects of host and organism are not considered.
Possible advantages to infection are not ordinarily considered.**

Non-pathogenic organisms are relegated to environmental microbiology and ordinarily not considered in medical microbiology.

The concept of one organism / one disease is strengthened.
Interaction of two or more microorganisms in disease causation is usually not considered.

The effects of environmental factors are not considered.

It does not stress host variation including inherited variation in response to infection.

Currently, about two billion (2×10^9) people, one third of the world's population, are infected with HBV. About 375 million (375×10^6) are chronic carriers and the rest have anti-HBs, anti-HBc, and other markers indicating infection.

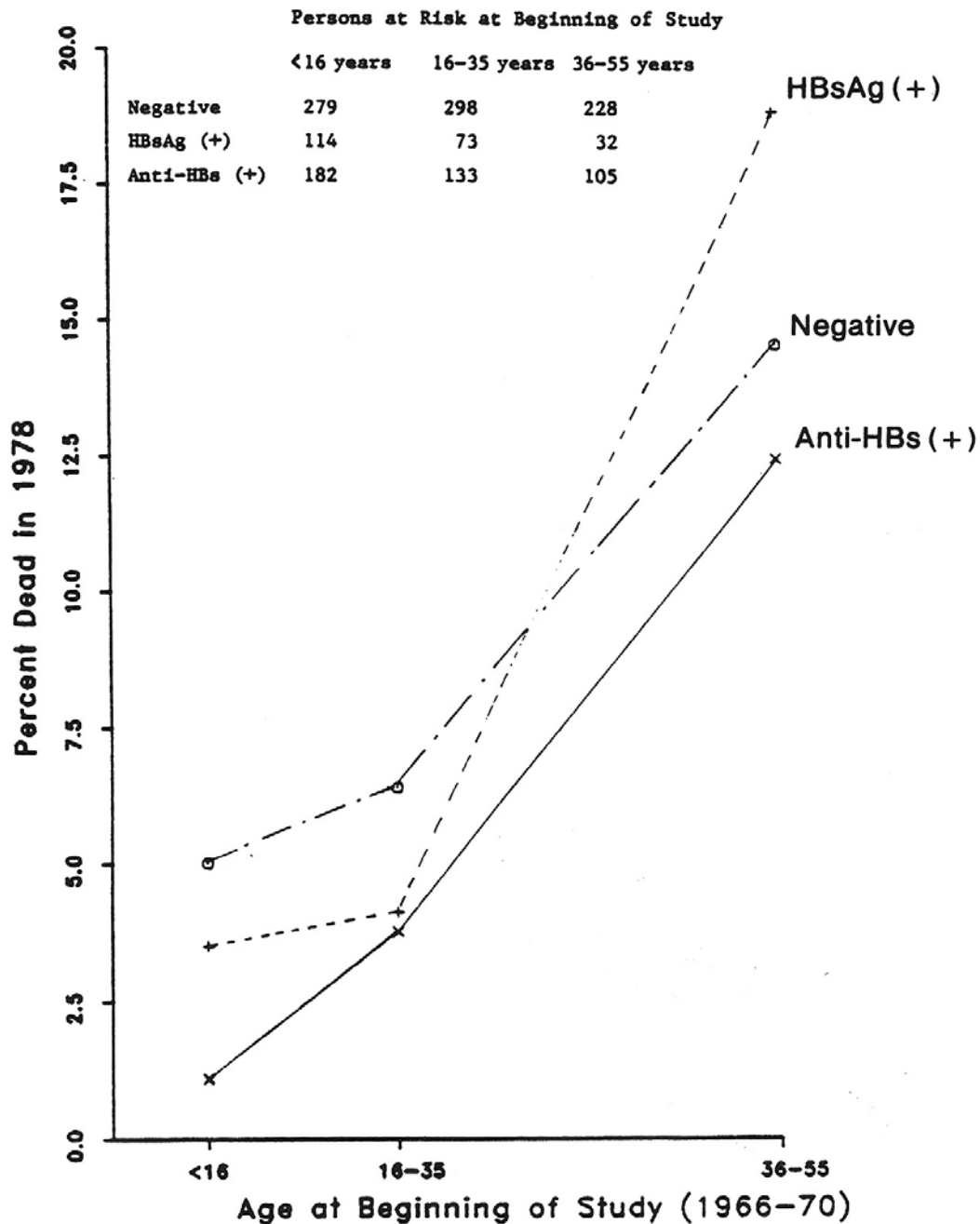
HBV is one of the most common infections in the world.

About 600,000 to 1,000,000 deaths per year
are attributable to the diseases associated with HBV.

PREDICTED DEATHS FROM PREVALENT CARRIERS OF HIV AND HBV

(H. Margolis, Center for Disease Control. Paper presented at Third International Conference on Therapies for Viral Hepatitis, Maui, 12/12/99)

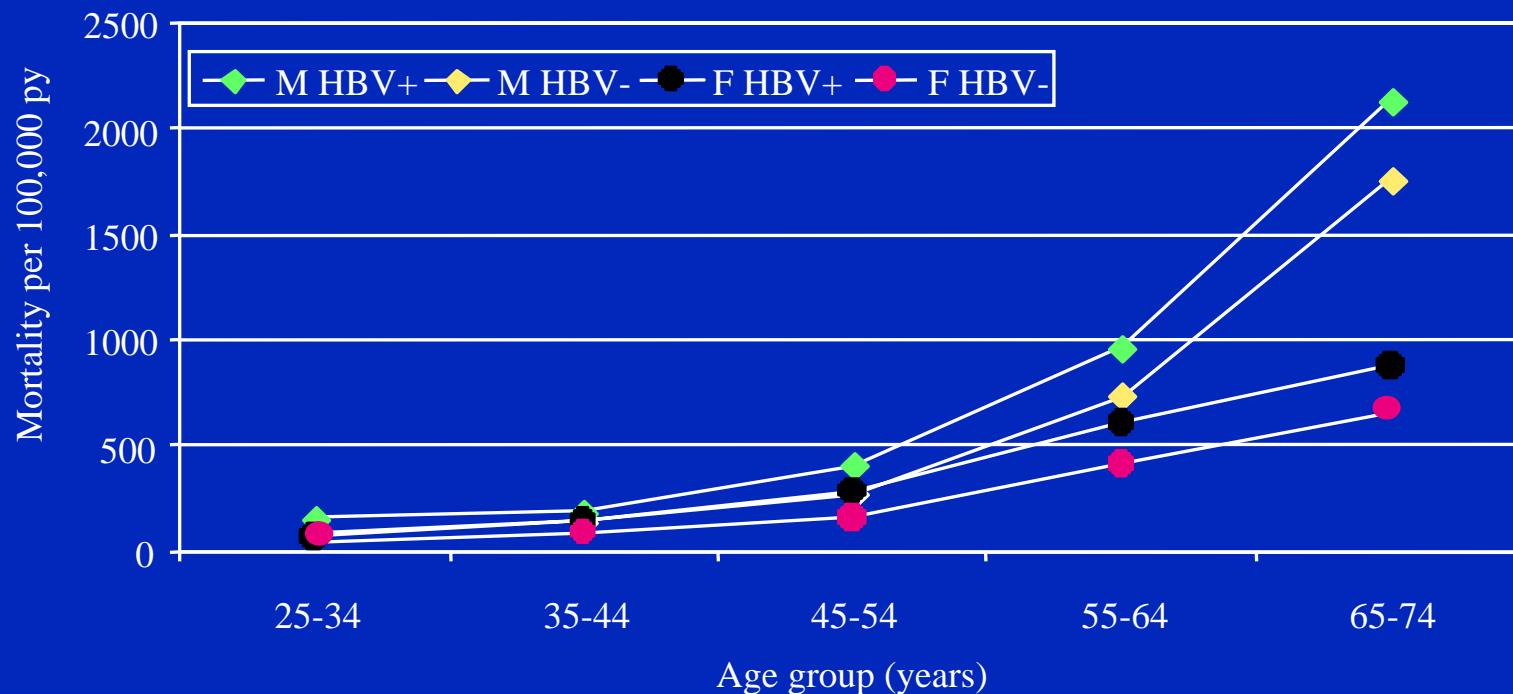
Virus	Number Infected (Millions)	Case Fatality Rate	Total Deaths (Millions)
HIV	34	100%	34
HBV	371	High 25%	92.8
		Low 15%	55.7



Responses to HBV of 1,444 individual in the Solomon islands in 1966-1970 compared with the mortality of these individuals in 1978. The inserted table show the number of individuals by age and HBV status at the beginning of the study.

W. T. Thomas London , B. Blumberg, R. Stevens, S. ShoferIn , J. Drew, J. Brunhofer, in
 Viral Hepatitis, edited by Wolf Szmuness *et al.* 1982

MORTALITY BY AGE, GENDER AND HBV RESPONSE HAIMEN CITY, CHINA



Mortality in 2003 of HBV carriers (darkened points) and non-carriers (open points) of males (squares) and females (circles) who were tested for HBV between February 1992 and December 1993.

G. Chen, W. Lin, F. Shen, U. Iloeje, T. London and A. Evans
Inter. J. of epid. 2004, in print

GENETIC HYPOTHESIS FOR THE HBV CARRIER STATE

Blumberg *et al* 1966

Susceptibility to the carrier state is, in part, controlled by an autosomal recessive gene termed Au^1 . Individuals homozygous for this gene (Au^1/Au^1) are phenotype $Au(1)$ and, when infected, are likely to become carriers.

Those who are homozygous for the alternate allele Au (Au/Au) or are heterozygotes (Au^1/Au), are phenotype $Au(0)$ and, if infected, are less likely to become carriers.

Summary of Calculations by Smith's and Li and Mantel's Methods for Cebu and Bougainville Families

Location	Types of Mating	No. of Families	Smith's Method			Li and Mantel's Method		
			No. of Recessive Children			Total No. of Children	Corrected Ratio	Standard Error
			Observed	Expected	Variance			
Cebu	Au(0) x Au(0)	24	33	32.705	8.069	85	0.2461	0.0585
Cebu	Au(1) x Au(0)	7	12	12.189	3.556
Bougainville	Au(0) x Au(0)	41	56	53.815	11.593	124	0.2527	0.0561
Bougainville	Au(1) x Au(0)	24	42	40.062	11.008

Microorganism Gene Affinity Clusters

Locus	Allele	Agent/Disease	Chrom	Function
MHC Class II	DRB1*1302	HBV chronicity (P) HBV response to interferon Malaria, cerebral (P) Pappiloma virus	Chrom 6	Immune response
VDR	tt	HBV chronicity (P)	Chrom 12	Vitamin D Receptor Binds Vit. D 1,25D3
	tt	TB Pulmonary (P)		
	TT	Leprosy, tuberculoid (P)		
	Tt	Leprosy, infection (P)		
	tt	Leprosy, lepromatous (P)		
	tt	Bone mineral density, lower Osteoporosis, increase risk Prostatic cancer (P) Inflammatory bowel disease		

Microorganism Gene Affinity Clusters (*cont.*)

Locus	Allele	Agent/Disease	Chrom	Function
TNF	G-308	HBV chronicity Malaria, cerebral Microcutaneous leish. Lepromatous leprosy Meningococcal Meningitis Trachoma Asthma	Chrom 6	Tumor Necrosis Factor
MBP	Codon 52	HBV chronicity SLE, HIV (?) Infections in childhood	Chrom 10	Mannose Binding Protein
SM-1 5q31-33		Schistosomiasis ? HBV chronicity	Chrom 5	Schist. Susceptibility
IL-10 Promoter	Mutat. - 108 Mutat. - 059	HBV chronicity HBV chronicity	Chrom 1	Immune response

CONTROL OF HEPATITIS B VIRUS IN CHINA

Z.Y. Xu, T.Q. Yan, S.J. Zhao, et al. Shanghai Medical University

“Infant HBV immunization has been implemented into public health service in China since 1986... the seropositivity for HBsAg was reduced from 16.3% (879/5397) of historical controls to 1.43% (70/4886) in cross-sectional study and 1.81% (210/11582) in a cohort study.”

HBV VACCINATION IN THE UNITED STATES

In the United States, the number of new HBV infections per year has declined from an average of **260,000 in the 1980s** to about **78,000 in 2001**. The highest rate of disease occurs in the 20-49 age group. Greatest decline is the consequence of the routine HBV vaccination program among children and adolescents. There are an estimated 1.25 million chronically infected Americans, of whom 20-30% acquired their infection in childhood.

CDC Website, 2004

HBV VACCINATION IN ALASKA, USA

- A universal childhood vaccination program was undertaken between 1981 and 1983 in **Native Americans in Alaska, USA** (McMahon, et al., 1996).
- Acute hepatitis B infection dropped from **215 cases/100,000** before the vaccination program, to **7 to 14 cases in 1993** after the program was in place. In 1995, **no cases were reported.**

Hepatitis B Virus Worldwide Vaccination Program

As of May 2003, 151 (79%) of 192 national members of the WHO had universal childhood vaccination programs. There are 89 member states that have been designated as having a high prevalence of HBV carriers. Sixty four (72%) have universal infant vaccination programs. It is the goal of the WHO to have vaccination programs in all countries by 2007.

Distribution of Australia Antigen (HBsAg) by Gender

	Total Number	Number Positive	Percent Positive
Marshall Islands, USTTPI			
Male	243	19	7.8
Female	226	14	6.2
Total	495	33	6.7
Cebu, Philippines			
Male	430	27	6.3
Female	334	10	3.0
Total	764	37	4.8
Manila, Philippines			
Male	138	6	4.3
Female	59	3	5.1
Total	197	9	4.6
Cashinahua, Peru			
Male	45	10	22.2
Female	44	6	13.6
Total	89	16	18.0

Blumberg, et al, Amer. J. Human Genetics 18, 594, 1966

PLATI, GREECE. NUMBER OF MALE AND FEMALE LIVE BIRTHS ACCORDING TO THE RESPONSES TO HBV OF PARENTS

Parent's response To HBV	Couples (No.)	Live births		Sex ratio
		Male	Females	
Either parent HBsAg + : anti-HBs –	33	60 (1.8 ± 0.2)	24 (0.7 ± 0.1)	250 (161,429)*
Both parents HBsAg - : anti-HBs –	29	51 (1.8 ± 0.2)	35 (1.2 ± 0.2)	146 (96,230)*
Both parents HBsAg - : either parent anti-HBs +	154	241 (1.6 ± 0.1)	222 (1.4 ± 0.1)	109 (91,131)*

*In parentheses, the 5 percent confidence limits.

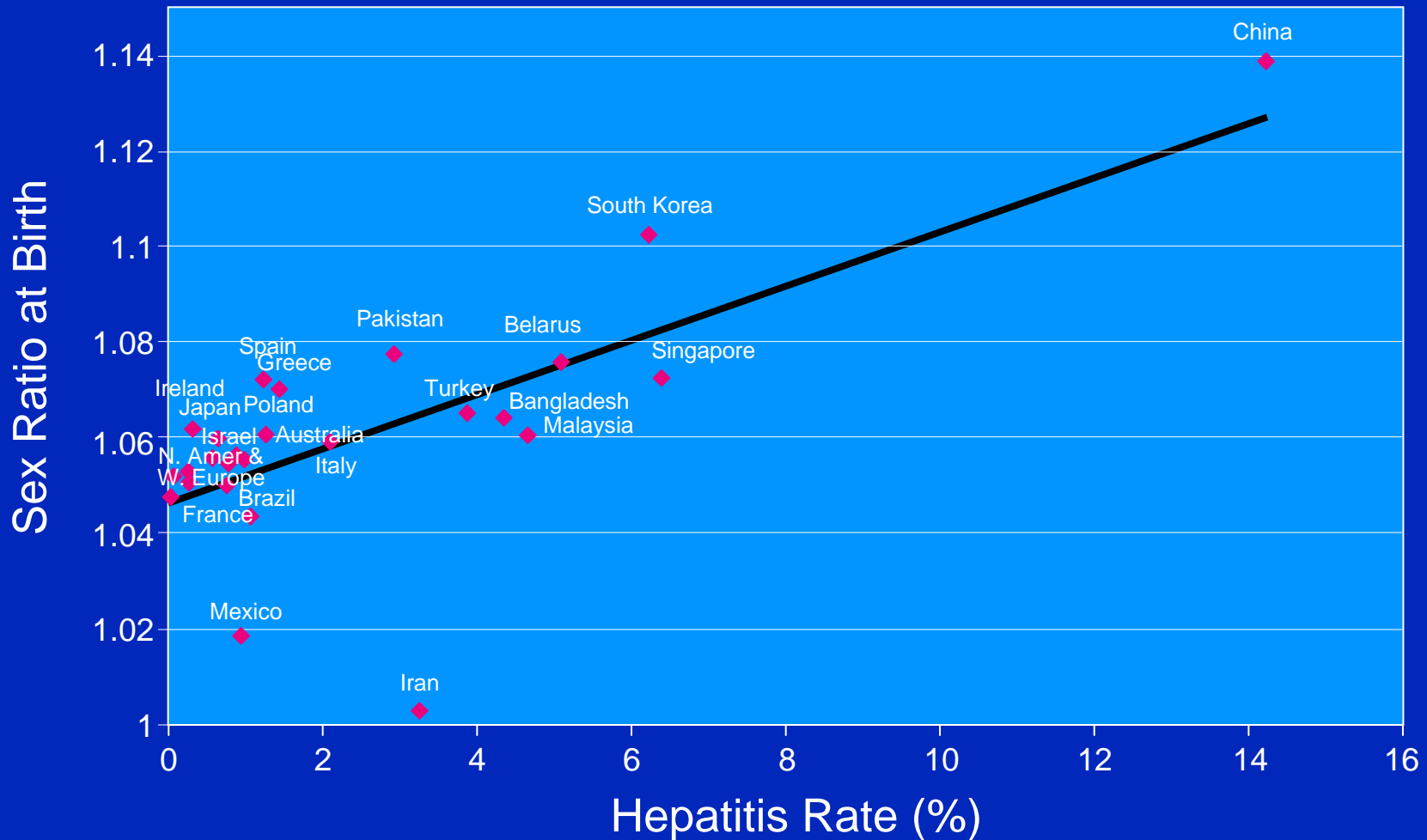
Blumberg, B.S. Sex differences in response to Hepatitis B Virus,
Arthritis and Rheumatism, 22, 1261, 1979

Hepatitis B and Sex Ratio: Individual Level Estimates

Location	HBV Status	Sons	Daughters	Sex Ratio
Greenland	Positive	64	60	1.07
Greenland	Negative	174	194	0.90
Kar Kar Island	Positive	63	54	1.17
Kar Kar Island	Negative	163	206	0.79
Greece 1	Positive	85	46	1.85
Greece 1	Negative	287	255	1.13
Philippines	Positive	66	41	1.61
Philippines	Negative	304	301	1.01
Greece 2	Positive	52	30	1.73
Greece 2	Negative	1006	955	1.05
France	Positive	20	12	1.66
France	Negative	149	122	1.22

Notes: This table shows sex ratios among the children of carrier and non-carrier parents in four regions. Data were collected by testing married women and, in all cases except for Greenland, their husbands for HBV. Detailed reproductive histories were also collected. The table represents all births to women in those samples, with generally more than one birth to each women. The last two studies (Greece 2 and France) were designed specifically to test the hypothesis that HBV affects offspring sex ratio, and were run after the original theory was expressed.

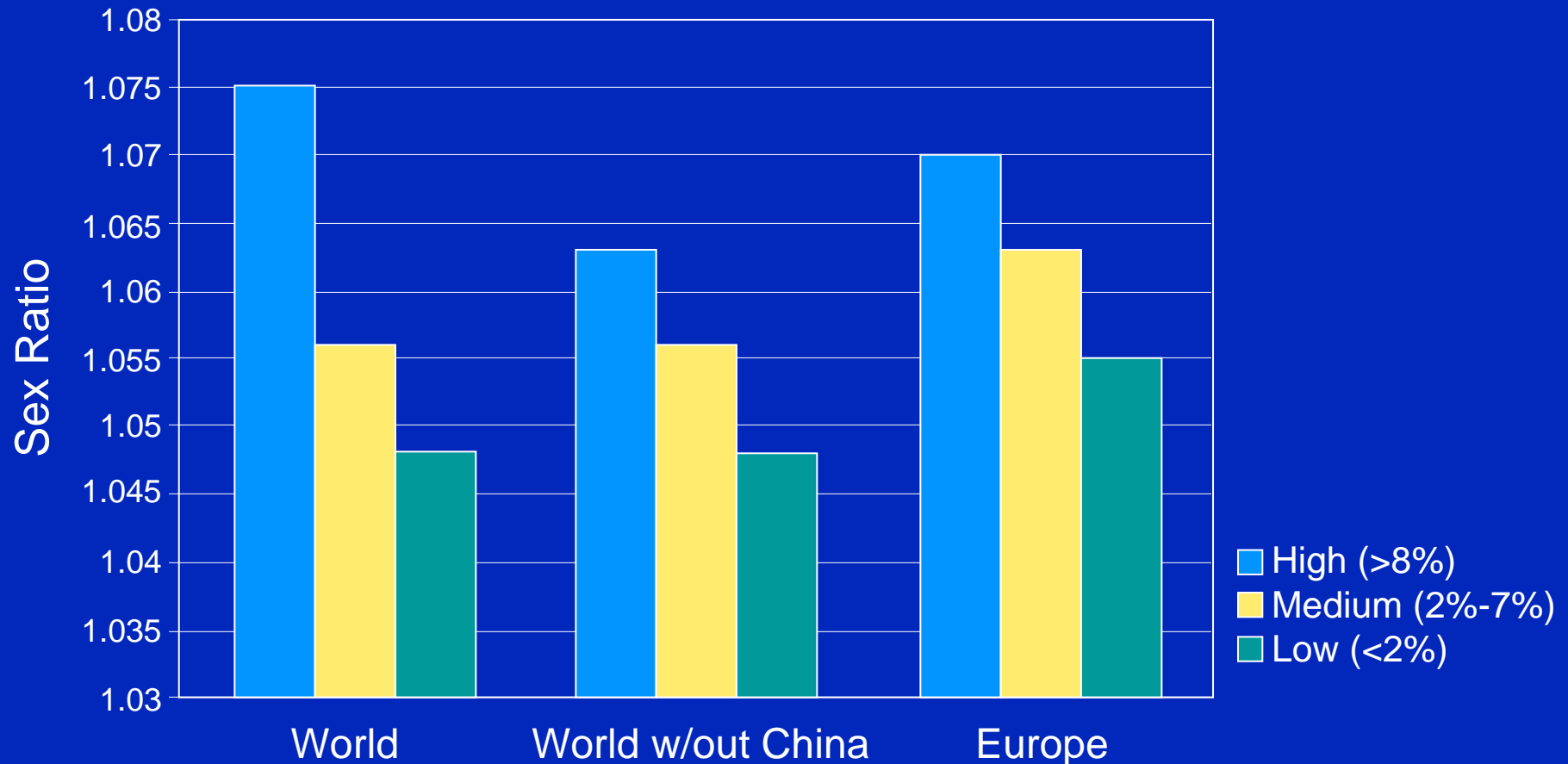
SEX RATIO AND HEPATITIS, WORLD



Notes: Sex ratio is number of boys for each girl. Only countries with more than 15,000 people used to calculate HBV prevalence are included. Citations for each country are in Appendix B.

Oster, E., Hepatitis B and the Case of the Missing Women, Presentation, October 12, 2004

SEX RATIO BY WHO HBV PREVALENCE

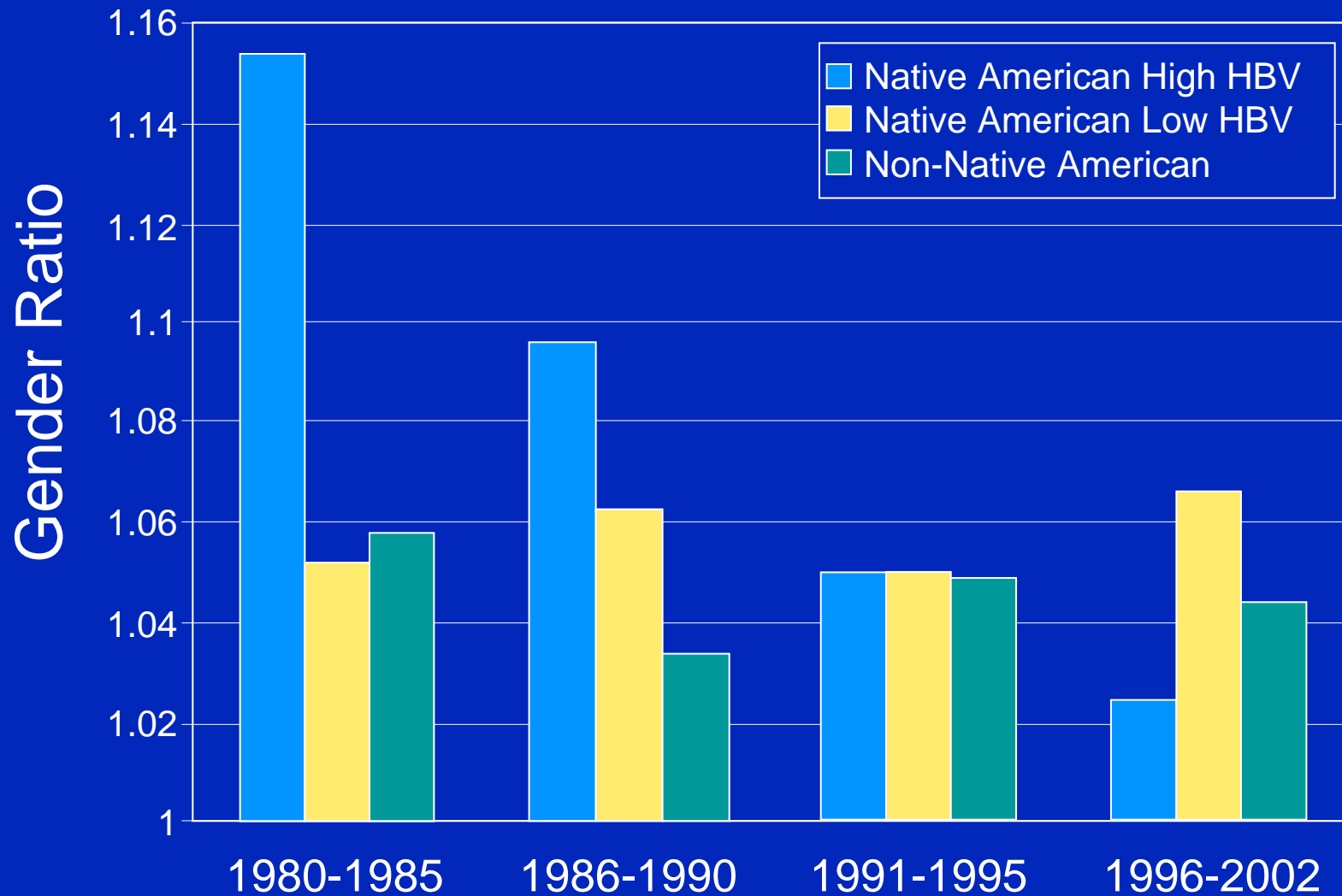


Notes: Sex ratio is number of boys for each girl. Sex ratio in each group is total number of boys born in that group divided by total number of girls.

PREVALENCE OF HBV IN POPULATIONS OF ALASKA

- High HBV prevalence in Inuit (Eskimo) Native Americans
- Low HBV prevalence in Indian Native Americans
- Low HBV prevalence in Alaskans who are not Native American
- Universal vaccination program (including catch-up) in early 1980's

CHANGES IN GENDER RATIO IN ALASKA BEFORE AND DURING VACCINATION PROGRAM



Oster, E., Hepatitis B and the Case of the Missing Women, Presentation, October 12, 2004

- HBV explains about 50% of the “missing” women overall:
over 90% in China, 11% in India
- Vaccination programs appear to decrease gender ratio

HBV and Iron in Down's Syndrome Patients With and Without HBsAg

	Hemoglobin g/100ml	Hematocrit %	Serum Iron μg/100ml	TIBC μg/100ml
HBsAg(+)				
Mean	15.2	44.2	163.7	250.4
SD	1.4	3.8	115.1	108.2
HBsAg(-)				
Mean	14.9	43.5	84.1	356.8
SD	1.4	3.6	33.6	144.8

Increased Hemoglobin, Hematocrit, Serum Iron and decreased Total Iron Binding Capacity (TIBC) in 20 Down's Syndrome patients with serum HBsAg compared to 20 without. The differences are significant.

Sutnick, Blumberg, Lustbader. Ann. Int. Med. 81, 855, 1974

Serum Iron Levels (mg/dl)

	<u>Downs Syndrome</u>			<u>Renal Dialysis</u>			<u>Senegal</u>		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
HBsAg (+)	164	-	164	114	214	145	77	81	79
HBsAg (-)	84	-	84	98	100	100	75	58	65
Number	40	-	40	40	117	220	81	112	193

Serum Iron levels in 1) Patients with Down's Syndrome 2) Patients on renal dialysis and 3) Residents of a rural community in Senegal, West Africa.

Blumberg in Szentivanyi and Friedman, Editors, Viruses, Immunity and Immunodeficiency, Plenum 1986

CONCLUSION

There is a nuanced, complex and non-intuitive interplay of many factors that determine the overall effects of HBV in a population. It is important to understand these as the vaccination programs proceed.