PREVENTION OF EMBRYONIC, FETAL, AND PERINATAL DISEASE

PREVENTION OF EMBRYONIC, FETAL, AND PERINATAL DISEASE

The John E. Fogarty International Center for Advanced Study in the Health Sciences

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Bethesda, Maryland

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PREFACE

The Fogarty International Center was established in 1968 as a memorial to the late Congressman John E. Fogarty from Rhode Island. It had been Mr. Fogarty's desire to create within the National Institutes of Health a center for research in biology and medicine dedicated to international cooperation and collaboration in the interest of the health of mankind.

The Fogarty International Center is a unique resource within the Federal establishment, providing a base for expansion of America's health research and health care to lands abroad and for bringing the talents and resources of other nations to bear upon the many and varied health problems of the United States.

As an institution for advanced study, the Fogarty International Center has embraced the major themes of medical education, environmental health, societal factors influencing health and disease, geographic health problems, international health research and education, and preventive medicine. Our commitment to the study of preventive aspects of human disease is expressed in the Fogarty International Center Series on Preventive Medicine.

Improvement in the health status of the American people will depend, in great measure, on the design and application of programs which place major emphasis on the preventive aspects of human disease. Although health authorities generally agree with this thesis, there is need for more precise definition of effective methods and programs of prevention, financial resources required to implement these programs, and priorities to be assigned to research in preventive methodology. The need to assemble expertise in this field, to elucidate mechanisms whereby the full impact of preventive medicine may be brought to bear on the solution of America's major health problems, has been expressed repeatedly in public statements by leaders throughout the health field.

In response to this need, the Fogarty International Center initiated a series of comprehensive studies of preventive medicine in order to review and evaluate the state of the art of prevention and control of human diseases, to identify deficiencies in knowledge requiring further research, including analysis of financial resources, preventive techniques, and manpower, and to recognize problems in application of preventive methods and suggest corrective action.

This monograph has been prepared by the Committee on Prevention of Fetal and Perinatal Diseases under the chairmanship of Dr. Robert Brent and represents the third volume of the Fogarty International Center Series on Preventive Medicine. While considerable progress has been made in the elimination of diseases affecting the fetus and newborn infant, the United States continues to rank below many other industralized nations in the prevention of fetal wastage and infant death. In 1974 infant mortality in the United States occurred at the rate of 16.5 per 1,000 live births, was the lowest ever recorded in this country, and resulted in an international ranking of 15th in this category. There are conspicuous differences in infant mortality rates among various ethnic groups in the United States and particular emphasis has been placed in this monograph on the definition of causes predisposing to fetal and infant mortality.

Low socioeconomic status of the mother is associated with a particularly high risk of complications and genetic, environmental, and physiologic variables contribute to unfavorable outcomes of pregnancy. The monograph analyzes causes of fetal and perinatal disease and recommends organizational and scientific methodologies that can now be applied toward their prevention. High risk pregnancies should be identified and monitored throughout gestation; when anticipated complications arise, expertise and facilities should be readily available in regional perinatal centers with specialized equipment and staff.

New knowledge will be required for further reduction in the rate of disabilities arising in early life. Of great potential are studies dealing with the understanding and control of fetal tissue development, refinement of noninvasive techniques for assessing the status of the developing fetus, improvement in the prevention and treatment of fetal and neonatal infections, development and regulation of facilities for the care of high risk pregnancies, development of genetic counseling services and other forms of consumer health education and modification of the health care delivery system which favors centralization of obstetrical and perinatal services. In view of high mortality from fetal and perinatal disease and the long-term care required for compromised infants, there are few areas of medicine where research and the application of existing knowledge will have greater benefits.

Milo D. Leavitt, Jr., M.D.
Director
Fogarty International Center

INTRODUCTION

The concept of this book entitled *The Prevention of Embryonic, Fetal, and Perinatal Disease* was developed by the staff of the Fogarty International Center as part of their program of developing new concepts that may lead to disease prevention. All the individual authors have appreciated the support and guidance provided by the Fogarty Center staff.

Many of the chapter authors were brought together to discuss and develop their material as part of this project. Through this monograph, governmental research programs which support scientific investigation have added another dimension by fostering the utilization of new scientific information and concepts in the preparation of a scientific document whose main purpose is the prevention of disease. My own (RLB) debt to Federal Government research support goes to the National Institutes of Health and the Energy Research and Development Agency, and I am certain that each of the scientists authoring this text can trace much of his creativity to government-supported research and training programs. In addition, all of us have had interaction with private foundations such as the National Foundation March of Dimes and even local groups that have supported research programs such as the very generous Harry Bock Charities, a group that has been related to research programs in developmental biology in Philadelphia. It is a great testimony to American generosity and ingenuity that research support has come from such diverse sources. This book is a culmination of just one piece of evidence that there is strength in our system and there should also be optimism among scientists even if there have been and will be periods when science seems out of style.

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INCIDENCE AND IMPACT OF FETAL AND PERINATAL DISEASE

Robert Sholtz, Hyman Goldstein, and Helen M. Wallace

INTRODUCTION

Handicapping conditions in children logically begin with factors which act singly or in combination to determine the progress and direction of growth. The earliest factors are genetic and those of the uterine environment. When these factors act favorably, the result is a normal, healthy child; when unfavorable, there is an adverse effect on the fetus, infant, or child ("pregnancy wastage" or "continuum of reproductive casualty").

Pregnancy wastage manifests itself as fetal death, neonatal death, congenital anomaly, birth injury, and a large range of handicapping conditions. The latter has been defined by the American Public Health Association as follows:

> *A child is to be considered handicapped if he cannot within limits play, learn, work or do the things other children of his age can do; if he is hindered in achieving his full physical, mental and social potentialities. The initial disability may be very mild and hardly noticeable, but potentially handicapping, or it may seriously involve several areas of function with the probability of lifelong impairment. The problem may appear to be primarily physical or perhaps emotional or social. Regardless of the nature of the chief manifestation, physical, emotional and social components are all factors at one time or another and in varying degrees, in most handicapping conditions of childhood* (Committee on Child Health, 1961.)

Environmental factors besides those of the uterine environment may handicap a child. It appears, however, that many of the factors which lead to perinatal death in some pregnancies may, in others, lead to congenital anomaly, birth injury or other potentially handicapping conditions.

MORTALITY

Comparing the extent of pregnancy wastage in different populations is difficult because investigators use varying criteria. The best measure is mortality, particularly that of live-born children. In addition, the extent of fetal mortality is under estimated because early pregnancy losses escape notice or go unreported.

Niswander and Gordon (1972) have written:

> *The magnitude of the problem of perinatal death is illustrated by the fact that until old age the risk of dying is highest during the perinatal period. While the general mortality rate for the U.S.A. approximates 9 per 1,000 population during the period 1955-65, the perinatal death rate is almost four times as great, approximately 35 per 1,000 live births. The age specific risk of dying does not again approach a rate of 35 per 1,000 until the 64th year is reached. Moreover, even at this age, the risks are not comparable, because the age specific risk extends over a one-year time span, while the risk of dying during the perinatal period is limited to about one-half, from 20 weeks gestation until 28 days after birth."*

TABLE 1. Estimate of Total Fetal Losses Based on Extrapolated Observations Among Private Patients

Gestational Age (weeks)	Probability of Fetal Death Per 1,000 Pregnancies During Period	Number of Fetal Deaths Expected Per 1,000 Conceptions at Time 0
0-3	112.1	112
4-7	82.4	73
8-11	67.1	55
12-15	28.2	21
16-19	10.7	8
20-23	8.9	7
24-27	2.1	2
28-31	4.3	3
32-35	2.0	1
36-39	6.9	5
40 or more	10.8	8
Total		295

Reprinted with permission from Erhardt (1963).

Fetal Mortality

Fetal death ratios per 1,000 live births for 1973 were 10.8 for whites, 18.6 for all others, and 12.2 for all races combined (Vital Statistics of the United States, 1974). The true rates appear to be much higher. From the twentieth week of gestation onward, the fetal death rates have been estimated by Erhardt (1963) to be 36.5 per 1,000 live births, by French and Bierman (1962) and Taylor (1970) to be 25.0.

The fetal loss according to gestational age as determined by these investigators is given in Tables 1 and 2.

TABLE 2. Estimated Probabilities of Fetal Death by Gestational Age

Gestational Age (weeks)	Probability of Fetal Death Per 1,000 Still Pregnant at Gestational Age	
	French*	Taylor†
0	—	160.1
4	237.3	160.1
8	144.8	105.3
12	80.5	59.5
16	37.4	35.1
20	24.4	24.4
24	16.1	16.8
28	13.0	13.6
32	10.2	10.1
36	7.4	7.1
40	6.8	5.1
44	—	11.6
48	—	17.9
52	—	111.1

—No estimate given.
*Taken from French and Bierman (1962).
†Taken from Taylor (1970).

Infant Mortality

Mortality rates for live born infants and children are more complete than for fetuses. Table 3 gives infant mortality and its components, neonatal mortality and post-neonatal mortality, for the United States in 1971. The provisional infant death rate for 1974 was 16.5 per 1,000 live births (14.7 for whites, 24.6 for nonwhites), the lowest annual rate ever recorded in the United States (Vital Statistics Reports, 1975). Table 4 gives an indication of the proportion of infant mortality which can be directly attributed to congenital anomalies, birth injuries, asphyxia of the newborn, immaturity, and other diseases of early infancy. Over 70 percent of all infant mortality was attributable to the above causes. Thus pregnancy wastage is by far the largest factor leading to death in the first year and accounts for at least 40,000 deaths to live-born infants each year in the United States.

Childhood Mortality

Mortality in children over one year of age is not as clearly a part of pregnancy wastage which is so important in fetal and infant mortality. Pregnancy wastage does continue to be a factor for some time though, as can be seen with respect to congenital malformations (Table 5). The rates for the other specific causes of death among infants (birth injury, asphyxia of new-

TABLE 3. Estimated Infant, Neonatal and Post Neonatal Mortality Rates Per 1,000 Live Births by Color for the United States, 1973

Color	Infant Mortality	Neonatal Mortality	Post Neonatal Mortality
White	15.8	11.8	3.9
All Other	26.2	17.9	8.3
Total	17.7	12.9	4.8

From Vital Statistics Reports (1974).

born, immaturity, other diseases of early infancy) drop to a low level after 1 year of age, and are not shown in Table 5. Congenital anomalies remain an important factor among causes of death at least through 14 years of age. Accurate estimates of the total problem are difficult to secure, as Kennedy (1967) has pointed out:

As other causes of pregnancy wastage are being brought under control, congenital malformations are rapidly emerging as one of the world wide problems in this field. Yet, though aware that this is so, we are at present unaware of the actual size of the problem. There is no standardization of recording or reporting and for this and other reasons many epidemiologic problems remain unsolved.

TABLE 4. Estimated Infant Mortality Per 1,000 Live Births and Proportionate Mortality by Selected Causes*, 1971

Cause of Death	Rate	Proportionate Mortality (per cent)
All Causes	19.2	100.0
Congenital Anomalies	2.8	14.6
Birth Injuries	0.5	2.6
Asphyxia of Newborn	2.4	12.5
Immaturity Unqualified	2.2	11.5
Other Diseases of Early Infancy	5.9	30.7
Subtotal		71.9
All Other Causes	5.4	28.1

*Selected causes—Eighth Revision, International Classification of Diseases, Adapted, 1965. Numbers as follows:

Congenital Anomalies	740-759
Birth Injuries	764-768 (.0-.3), 772
Asphyxia of Newborn, Unspecified	776.9
Immaturity, Unqualified	777
Other Diseases of Early Infancy	Remainder of 760-768
All Other Causes	All causes exclusive of 740-768

Taken from Vital Statistics Reports (1972).

TABLE 5. Death Rates From Congenital Anomalies* and All Causes Per 1,000 Population and Proportionate Mortality by Age, 1968

Cause of Death	Age in Years 1-4	5-9	10-14	15-17
Congenital Anomalies	0.09	0.03	0.02	0.02
All Causes	0.95	0.43	0.42	1.09
Proportionate Mortality (percent)	9.5	7.0	4.8	1.8

*Categories 740-759 from the Eighth Revision of the International Classification of Diseases, 1965 adapted.
Taken from Werner et al. (1971).

TABLE 6. Incidence of Congenital Anomalies as Reported in Research Studies Done in Britain

Authors	Locality	Period	Source of Statistics	No. of Births	Number Affected	Percentage Affected	Remarks
Slater et al	England	1963	College of G.P. Survey	1,038	23	2.21	January results only: LB and SB
Emerson	Aldershot	1961	Hospital records	1,374	25	1.81	
Stevenson et al	Belfast	1957	Examination and re-examination after one year	8,519	120	1.40	LB and SB. Gross anomalies
Cheeseman and Froggat	Belfast	1960-61	W.H.O. forms	28,091	544	1.93	Quoted by Stevenson et al
McKeown and Record	Birmingham	1950-52	Special cards	56,760	1,231	1.73	1,221 SB
Charles	Birmingham	1949	Special cards	19,711	357	1.81	"Probable underreporting"
Leck	Birmingham	1957-63	Hospital records and Home Visitors' reports	147,500	1,238	0.84	
Leck and Millar	Birmingham	1957-61	Hosp. and Pub. Hlth. Dept. records, H.V. reports	102,042	939	0.92	LB and SB
Corner	Bristol	1960-61	Hospital records	8,059	236	2.92	
Coffey and Jessop	Dublin	1953-54	Questionnaire and exams.	12,552	204	1.63	
Coffey and Quinn	Dublin	1965	Hospital deliveries Home deliveries	18,971 2,276	260* 30*	1.37 1.27	
(Simpson Maternity Hospital)	Edinburgh	1938-48 1955-63	Annual Reports	66,532	2,088	3.14	LB 63,666 CM 1706 or 2.68% SB 2,866 CM 382 or 13.32%
(Elsie Inglis Hospital)	Edinburgh	1948-49	Annual Reports	676	55	8.13	
Dean	Edinburgh		Individual examination	11,548	348	3.05	
Nelson	Edinburgh		Individual examination	8,648	496*	5.74 1.50	Total Major
Ward and Irvine	Exeter	1954-62	Welfare clinics and special enquiries	10,599	343	3.21	"Substantial abnormalities"
Landsman et al	Glasgow	1960-61	Hospital records and follow-up	2,542 48	45 11	1.77 22.91	LB SB
Craig	Leeds	1947-64	Hospital records	35,750	1,074	3.00	
Moss	Leicester	1953-62	Midwives, HVs and Clinic	46,312	921	1.99	77 had more than one severe CM
Malpas	Liverpool	1923-32	Hospital records	13,964	294	2.11	
Smithells	Liverpool		Hospital observation	2,688	88*	3.27	

Authors	Locality	Period	Source of Statistics	No. of Births	Number Affected	Percentage Affected	Remarks
Carter	London	1943-49	Hospital observation	14,283	219	1.47	LB and SB
Landtman	London	1945-48	Hospital observation	3,593	73	2.03	
Book and Fraccaro	London	1947-51	Maternity registers	20,151	609	3.02	Two hospitals
Pleydell	Northamptonshire	1944-57	Special register	60,890	603	0.99	Only 6 major groups CM included
Griffin and Sorrie	Reading	1958-63	Varied	12,951	393	3.04	
Stark	South Shields	1944-50	Hospital records	4,444	62*	1.39	
McDonald	Watford, St. Albans	1952-55	Personal interviews	3,216	50	1.58	Major
					72	2.37	Minor

Note: CM—Congenital malformation LB—Live births SB—Stillbirths NND—Neonatal deaths
*Signifies the figure has been calculated from the authors' data
Taken from Kennedy (1967).

TABLE 7. Incidence of Congenital Anomalies as Reported in Research Studies Done in Europe, excepting Germany

Authors	Locality	Period	Source of Statistics	No. of Births	Number Affected	Percentage Affected	Remarks
Reiffenstuhl	Austria, Graz	1946-51	Hospital records	38,687	105	0.27	Gross cases, "visible without special examination"
Fink	Austria, Vienna	1934-53	Univ. Obstetric Clinic	35,999	413	0.74	679 twins, 10 triplets
Elsner-Mackay	Austria, Wels	1945-62	Hospital records	30,000	81*	0.27	Major cases
Derom	Belgium	not stated	Hospital records	29,696	366	1.61	
Heyne	Belgium	1958-62	Inspector of Hygiene	554,703	3,363	0.61	
			and Doctors' reports	186,253	1,632	0.88	
Radanov et al	Bulgaria			8,022	118	1.47	
Bovev et al	Bulgaria, Sofia	1954-61	Hospital records	16,276	200	1.22	
Houstek et al	Czechoslovakia	1958-60	Registration	39,000	559	1.43	LB only
Kucera	Czechoslovakia		Clinic records	678,132	7,526	1.10	
Kucera et al	Czechoslovakia	1960-61	W.H.O. study	20,074	348	1.73	Quoted from Stevenson, A.C., et al
Schnellerova et al	Czechoslovakia, Brno	1957-60	University Neonatal Clinic	19,305	329	1.70	
Biering-Sorensen	Denmark, Copenhagen	1962	Health visits or supervision	6,485	75	1.16	
Buchi	Denmark, Copenhagen	1911-49		167,940	2,619	1.56	Quoted by Book and Fraccaro

Authors	Locality	Period	Source of Statistics	No. of Births	Number Affected	Percentage Affected	Remarks
Pedersen et al	Denmark, Copenhagen	1959-60		1,212	26	2.14	
Villumsen and Zachau-Christiansen	Denmark, Copenhagen	1959-61	Pediatrician's examination	1,707	61	3.57	
Stahler	Europe	1959	40 Clinic records in different countries	65,758	942	1.43	
Hirvensalo and Hjelt	Finland			14,091	606*	4.30	
Saxen and Haro	Finland	1957-62	Official questionnaire to maternity hospitals	504,742	9,398	1.86	Includes 7,777 SB with 1,038 CM, 13.34%
Klemetti	Finland, Keski Soumi	1963-64	Maternity Health Centers	3,674	103	2.80	Diagnosis by M.D. and/or pediatrician
Alison	France	1953-59	18 Maternity Hospitals	4,479	221	4.93	13 Parisian hospitals, 5 provincial
Ravina et al	France	1945-52	Hospital records	18,303	167	0.91	
Baron et al	France, Dijon	1950-58	Maternity register	13,403	162	1.21	
Azer	France, Lyon	1927-40	Maternity register	23,841	296	1.13	
Turpin	France, Paris	1941-50	Maternity register	78,844	622*	0.84	
Tholen	Holland, The Hague	1944-46	Obstetric Clinic	1,833	66	3.60	
Kovacs and Mackay	Hungary, Baja	20 yrs.	Hospital records	12,232	158	1.29	
Horn et al	Hungary, Budapest	1953-63	Clinic records	22,592	111	1.16	Major CM, single births
Nagy et al	Hungary, Debrecen	1947-58	Hospital records	42,988	774	1.84	
Cocozza and Tiso	Italy		Clinic records	3,200	52	1.62	
Nobili	Italy	1950-63		8,227	148	1.79	
Vignali	Italy, Brescia	1943-60	Hospital records	28,170	231	0.82	
Leone	Italy, Cagliari	1935-60	Hospital records	33,682	245	0.73	
Campli and Pedone	Italy, Foggia	1937-59	Hospital records	14,672	172	1.17	
Greco et al	Italy, Gargano	1957-61	Special examination	1,435	48	3.35	
Beolchini	Italy, Milan	1942-62	Hospital records	85,976	1,185	1.35	
Toricelli et al	Italy, Milan	1950-61		24,004	617	2.57	Quoted by Avezzu and Vinci
Avezzu and Vinci	Italy, Milan	1960-64	University Clinic	35,390	162	0.45	Major cases only
Ferrario and Fortuna	Italy, Novara	1930-49	Hospital records	9,474	72	0.76	Quoted by Book and Fraccaro

Authors	Locality	Period	Source of Statistics	No. of Births	Number Affected	Percentage Affected	Remarks
Carollo et al	Italy, Palermo	1957-64	Clinic records	6,669	99	1.48	
Spoto	Italy, Parma	1938-47		8,228	70	0.85	Quoted by Book and Fraccaro
Piccioni	Italy, Rome	1936-50	Obstetric Clinic	53,567	418	0.78	
Livadiotti et al	Italy, Rome	1949-62	Hospital records	37,853	742	1.96	
Calvani	Italy, Rome	1956-60	Hospital observation	15,233	359	2.35	
Maggiore	Italy, Rome	1956-58	Official records	2,660,990	4,120	0.15	1,311 SB or NND
Bologna	Italy, Rome		Hospital records	38,812	299	0.77	Major cases only
Aicardi et al	Italy, Sassari	1936-65	Clinic records	18,676	262	1.40	
Dellepiane and Colla	Italy, Torino	1949-55		7,991	61	0.76	Quoted by Book and Fraccaro
Avanzini and Girando	Italy, Torino	1953-58	Hospital records	6,465	88	1.36	
Morra and Cremona	Italy, Torino	1956-62	Hospital records	20,908	240	1.14	
Morandi and Marchesoni	Italy, Trento	1960-62	Hospital records	4,085	38	0.93	
Colucci and Tosolini	Italy, Udine	1950-63	Hospital records	16,217	94	0.57	
Kolbas	Jugoslavia, Croatia		Special examination	1,706	119	6.97	All babies at birth; nurslings 9.5%
Cupic et al	Jugoslavia, Lyubljana	1960-61	W.H.O. study	8,888	171	1.92	Quoted from Stevenson, A.C., et al
Kesic and Sestak	Jugoslavia, Zagreb	1960-61	W.H.O. study	8,416	107	1.27	Quoted from Stevenson, A.C., et al
Bjoro and Iversen	Norway	1944-58		39,848	394	0.98	
Mosing	Poland	1955-61	Hospital records	5,535	70	1.26	
Kobielowa et al	Poland, Krakow	12 yrs.	Clinic records	18,000	47	0.26	
Zytkiewicz et al	Poland, Lublin	10 yrs.	Clinic records	18,537	617	3.32	
Jaworska	Poland, Warsaw	1947-58	Clinic records	17,767	474	2.66	LB and SB
Roszkowski and Kietlinka	Poland, Warsaw		Clinic records	10,971	221	1.94	
Popa and Iliescu	Rumanian	1960-63	Clinic records	6,890	177	2.5	
Gonzalez-Coviella	Spain, Madrid	1963-64	Clinic records	20,221	271	1.34	
Monero et al	Spain, Madrid	1960-61	W.H.O. study	19,714	264	1.32	Quoted from Stevenson, A.C., et al

Authors	Locality	Period	Source of Statistics	No. of Births	Number Affected	Percentage Affected	Remarks
Fiuza Perez	Spain, Santander		Two pediatric institutions	31,500	690	2.19	31,500 children in the institutions, obviously no lethal defects involved
Hedberg et al	Sweden, Goteborg	1954-58	Prenatal Care Center	2,952	61	2.06	
Book	Sweden, Lund	1927-46	Maternity register	44,109	589	1.33	
Pfiffer	Switzerland, Basel	1920-33	Hospital records	25,241	370	1.46	Quoted by Sievers
Da Rugna	Switzerland, Basel	1953-62	Inspection with consultation	37,484	313	0.83	Severe cases only
Pomerants and Chukanina	U.S.S.R., Andizhan	9 yrs.		30,034	382	1.27	Mostly limbs affected
Dedukh and Lankovits	U.S.S.R., Moscow		Hospital records	47,936	448	0.93	

Note: CM—Congenital malformation LB—Live births SB—Stillbirths NND—Neonatal deaths
*Signifies the figure has been calculated from the authors' data
Taken from Kennedy (1967).

TABLE 8. Incidence of Congenital Anomalies as Reported in Research Studies Done in Germany

Authors	Locality	Period	Source of Statistics	No. of Births	Number Affected	Percentage Affected	Remarks
Mischel	Altona	1930-61	Hospital records	40,270	636	1.58	
Pereyma	Bamberg	1940-48		18,995	220	1.16	
Eichmann and Gesenius	Berlin and environs	1911-50	Hospital records	474,950	3,016	0.63	55 Hospitals
Prager	Berlin	1928-37	Hospital records	23,132	311	1.34	Quoted by Sievers
Kuhnelt and Rotter-Pool	Berlin	1934-54	Hospital records	44,291	514	1.11	
Ockel and Klemm	Berlin	1956-63 1960-64	Potsdam Hospital Friedrichsheim	12,320 15,922	145 57	1.18 0.36	
Schenk	Berlin	1938-41	Hospital records	11,077	366	3.30	
Winter and Patz	Berlin and environs	1950-56	Hospital and Clinic records	201,692	1,775	0.88	
Schubert	Berlin Moabit	1950-57	Inspection, pediatric consultation, obligatory P.M.s	5,314	112	2.10	
Buurman et al	Bonn, Celle, Gottingen, Leipzig	1901-56	Maternity register	240,691	2,667	1.11	