1.2 MODEL WITH AGE AS A CONTINUOUS VARIABLE

$$h=\lambda e^{\beta.l'+\varkappa.K}$$

Where:
β=Parameter for the strength of the effect of age.
π=Parameter for the abruptness of the start of fall.
λ=Age (now a continuous explanatory variable).
This model fits a smooth curve that is almost constant at first and then starts to fall with an abruptness depending on the value of π. The best estimate for π was 13.1; addition of lower order polynomials did not improve the fit, which means that a rise in fecundity of younger women is not supported by our data. The log likelihood was 3493.8.

1.3 CRITICAL AGE MODEL

$$h=\lambda e^{\beta.m+\varkappa.K}$$
$$m=(l-\gamma|l>\gamma)$$

Where:
λ=Critical age (age where the fall starts).
β=Rate of fall after the critical age.
m=Number of years older than critical age, or zero if younger.
Only discrete values of the critical age were investigated. The value with the maximum likelihood was selected. Therefore standard errors could not be calculated.

Figure 3 shows the baseline hazards (λ). The relative hazards ($e^{\beta.m+\varkappa.K}$) are indicated by the line in figure 2. The estimates were $\gamma=31$, $\beta=-0{\cdot}136$, and $\varkappa=0{\cdot}272$. The log likelihood was 3491.9 with the same degrees of freedom as model 1.2. The estimated hazard of a certain woman in a certain cycle (h) can be calculated by multiplication of the baseline hazard (λ), depending on the number of the cycle and the relative hazard ($e^{\beta.m+\varkappa.K}$) depending on the age and clinic.

We realise that the fact that our population consisted of a mixture of fertile and infertile women is theoretically incompatible with the use of the Cox regression model.[17] The mixed character of the population should lead to a constant shift in the proportional hazards between young and old women with time (insemination cycle). However, modelling interaction of the parameters with time (that is, assuming β and γ are different in a first and second period of time) does not lead to a significantly better fit. We therefore conclude that the theoretical incompatibility does not cause problems in this particular analysis.

2.1 LOGISTIC MODEL FOR PROBABILITY OF SUCCESSFUL PREGNANCY

$$p=\frac{e^{a+\beta.m+\varkappa.K}}{1+e^{a+\beta.m+\varkappa.K}}$$

Where p is the probability of successful pregnancy. The other symbols have the same meaning as in model 1.3. The estimator for difference between clinics ($\varkappa$) was not significant. The parameters of the model without $\varkappa$ were $\alpha=2.13$, $\beta=-0{\cdot}25$, and $\gamma=30$.

1 Schwartz D, Mayaux MJ. Female fecundity as a function of age. *N Engl J Med* 1982;**306**:404-6.
2 Bongaarts J. Infertility after age 30: a false alarm. *Fam Plann Perspect* 1982;**14**:75-8.
3 Stein ZA. A woman's age: childbearing and child rearing. *Am J Epidemiol* 1985;**121**:327-43.
4 Kaplan EK, Meier P. Non-parametric estimation from incomplete observations. *Journal of the American Statistics Association* 1958;**53**:457-81.
5 Cox DR. Regression models and life tables. *Journal of the Royal Statistical Society* 1972;**34**(series B):187-202.
6 Aitkin MD, Anderson AO. *Statistical modelling in GLIM*. Oxford: Clarendon Press, 1989.
7 Spira A. The decline of fecundity with age. *Maturitas* 1988;suppl 1:15-22.
8 Van Noord-Zaadstra BM, Karbaat J, te Velde ER, Habbema JDF, van der Maas PJ. The study of risk habits in reproductive and perinatal epidemiologic research: the use of a donor inseminated population of women. *Paediatr Perinat Epidemiol* 1989;**3**:11-8.
9 Emperaire JC, Gauzere-Soumireu E, Audebert AJM. Female fertility and donor insemination. *Fertil Steril* 1982;**37**:90-3.
10 Yoshimara Y, Hosoi Y, Atlas SJ, Wallach EE. Effect of clomiphene citrate on in vitro ovulated ova. *Fertil Steril* 1986;**45**:800-4.
11 Howe G, Westhoff C, Vessey M, Yeates D. Effects of age, cigarette smoking, and other factors on fertility: findings in a large prospective study. *BMJ* 1985;**290**:1697-1700.
12 Menken J, Trussell J, Larsen U. Age and infertility. *Science* 1986;**233**: 1389-95.
13 Harrison KL, Breen TM, Hennesy JF, *et al*. Patient age and success in a human IVF programme. *Aust N Z J Obstet Gynaecol* 1989;**29**:326-8.
14 Medical Research International Society for Assisted Reproductive Technology, the American Fertility Society. In vitro fertilization—embryo transfer (IVF-ET) in the United States: 1989 results from the IVF-ET registry. *Fertil Steril* 1991;55:14-23.
15 Sauer MV, Paulson RJ, Lobo RA. A preliminary report on oocyte donation extending reproductive potential to women over 40. *N Engl J Med* 1990;**323**:1-60.
16 Berkowitz GS, Skovron ML, Lapinski RH, Berkowitz RL. Delayed childbearing and the outcome of pregnancy. *N Engl J Med* 1990;**322**:659-64.
17 Lamb EJ, Hagen N, Pauker SG. The mean interval to conception: a measure of utility for the analysis of decisions involving fertility. *Am J Obstet Gynecol* 1989;**160**:1470-8.

(Accepted 18 April 1991)

Unrecognised HIV related deaths

Anna McCormick

Office of Population Censuses and Surveys, London WC2B 6JP
Anna McCormick, FFPHM, *senior medical statistician*

BMJ 1991;**302**:1365-7

Abstract

***Objectives*—To establish whether follow up of deaths from selected HIV related causes could increase the number of cases of HIV infection reported to the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC), and to estimate the proportion of deaths among HIV positive men that occurred in men who were not known to be HIV positive at the time of death by the person who signed the death certificate.**

***Design*—Follow up of draft death entries received by the Office of Population Censuses and Surveys on which one of 11 medical or external causes likely to be related to HIV was stated; letters were sent to the people who signed the certificates. The respondents were invited to report men known to have been HIV positive who were not already on the CDSC register.**

***Setting*—England and Wales.**

***Subjects*—Men aged 15-54 who died in February 1989 to July 1989 with one of the 11 selected HIV related diseases as cause of death on their death certificates.**

***Main outcome measures*—Number of men reported to the CDSC as a result of this follow up; estimate of excess deaths due to an HIV related cause; estimate of the proportion of excess deaths that occurred in those who were not known to be HIV positive at the time of death.**

***Results*—Replies were received for 473 deaths (86%). Forty were for men known to have been HIV positive, 31 of whom had been reported to CDSC by the time they died; six were subsequently reported. The respondent did not know that the deceased was HIV positive for 20 (35%) of the 57 excess deaths in men for whom one of the medical causes was stated and 41 (93%) of the 44 excess deaths in men for whom one of the external causes was stated.**

***Conclusion*—Follow up of death registrations is not an efficient way of increasing the number of cases of HIV infection reported to CDSC. Between 35% and 60% of HIV positive people for whom certain causes are stated may be dying without HIV positivity having been diagnosed. There may be implications for those caring for people with these conditions and those who carry out postmortem examinations.**

Introduction

On p 1375 I report that mortality from 95 selected causes increased by 25% between 1984 and 1989 among single men aged 15-54 and there is evidence that

TABLE I—*Response to inquiry about deaths due to medical and external causes and number of men known to have been HIV positive reported or not reported to CDSC*

Disease (ICD code)	No of letters sent	No (%) of replies received	No reported	No not reported (No subsequently reported*)
Medical causes				
Septicaemia (038)	12	11 (92)	1	
Pneumocystosis (136.3)	11	10 (91)	6	4 (3)
Malignant neoplasm of lip, oral cavity, and pharynx (140-149)	89	80 (90)		
Malignant neoplasm of skin (173)	5	4 (80)	2	
Other malignant neoplasm of lymphoid and histiocytic tissue (202)	111	99 (89)	9	
Lymphatic leukaemia (204)	52	45 (87)		1 (1)
Pneumonia, organism unspecified (486)	24	22 (92)	13	1
Total	304	271 (89)	31	6 (4)
External causes				
Drug dependence (304)	21	18 (86)		
Poisoning by analgesics (965)	107	95 (89)		2 (1)
Poisoning by psychotropics (969)	70	57 (81)		
Poisoning by other and unspecified drugs (977)	46	32 (70)		1 (1)
Total	244	202 (83)		3 (2)

CDSC=Communicable Disease Surveillance Centre.
ICD=International Classification of Diseases.
*Subsequently reported cases were included in the total.

TABLE II—*Estimated excess deaths from possible HIV related causes in men aged 15-54 years in England and Wales in 1989*

Disease (ICD code)	Observed deaths	Expected deaths*	Estimated excess deaths	Proportion of observed deaths (%)
Medical causes				
Septicaemia (038)	21	23	−2	
Pneumocystosis (136.3)	14	2	12	86
Malignant neoplasm of lip, oral cavity, and pharynx (140-149)	211	167	44	21
Malignant neoplasm of skin (173)	25	20	5	20
Other malignant neoplasm of lymphoid and histiocytic tissue (202)	337	275	62	18
Lymphatic leukaemia (204)	111	117	−6	
Pneumonia, organism unspecified (486)	62	14	48	77
Total	781	618	163	21
External causes				
Drug dependence (304)	135	90	45	33
Poisoning by analgesics (965)	256	206	50	20
Poisoning by psychotropics (969)	137	104	33	24
Poisoning by other and unspecified drugs (977)	81	77	4	5
Total	609	477	132	22
Overall total	1390	1095	295	21

ICD=International Classification of Diseases.
*Based on 1984 rates.

TABLE III—*Comparison of estimated excess deaths from possible HIV related causes and deaths known to be related to HIV in men aged 15-54 years in the six months from February to July 1989*

Disease (ICD code)	Observed deaths	Estimated excess deaths*	Deaths in men known to have been HIV positive	Proportion of excess deaths in men not known to have been HIV positive (%)
Medical causes				
Septicaemia (038)	11		1	
Pneumocystosis (136.3)	10	9	10	
Malignant neoplasm of lip, oral cavity, and pharynx (140-149)	80	17		17 (100)
Malignant neoplasm of skin (173)	4	1	2	
Other malignant neoplasm of lymphoid and histiocytic tissue (202)	99	18	9	9 (50)
Lymphatic leukaemia (204)	45		1	
Pneumonia, organism unspecified (486)	22	17	14	3 (18)
Total	271	57	37	20 (35)
External causes				
Drug dependence (304)	18	6		6 (100)
Poisoning by analgesics (965)	95	19	2	17 (89)
Poisoning by psychotropics (969)	57	14		14 (100)
Poisoning by other and unspecified drugs (977)	32	2	1	1 (50)
Total	202	44	3	41 (93)
Overall total	473	101	40	61 (60)

ICD=International Classification of Diseases.
*By applying the proportional excess deaths from table II to observed deaths during the study.

at least some of this increase was associated with the HIV epidemic and is only partly accounted for by deaths attributed to AIDS or HIV infection or reported to the Communicable Disease Surveillance Centre (CDSC).[1] In the present paper I describe a study to determine whether follow up of deaths for which one of 11 causes related to HIV infection was given on the death certificate would increase the number of reported cases of HIV infection. The study also aimed at determining the proportion of HIV positive men not known to be seropositive at the time of death.

Methods

A letter was sent to the people who signed the death certificates of all men aged 15-54 in England and Wales with one of 11 causes likely to be related to HIV mentioned on their death certificate; it asked whether the deceased had been HIV positive. For any men known to have been HIV positive but not reported to CDSC an invitation to report was sent.

The total number of expected deaths from each cause in 1989 was calculated by applying the 1984 rate to the 1989 population in each five year age group. The excess in 1989 was assumed to be the number of deaths related to HIV. The proportion of excess deaths in 1989 was applied to the number of deaths due to each cause during the study period to estimate the number of excess deaths which would be expected in the study.

Results

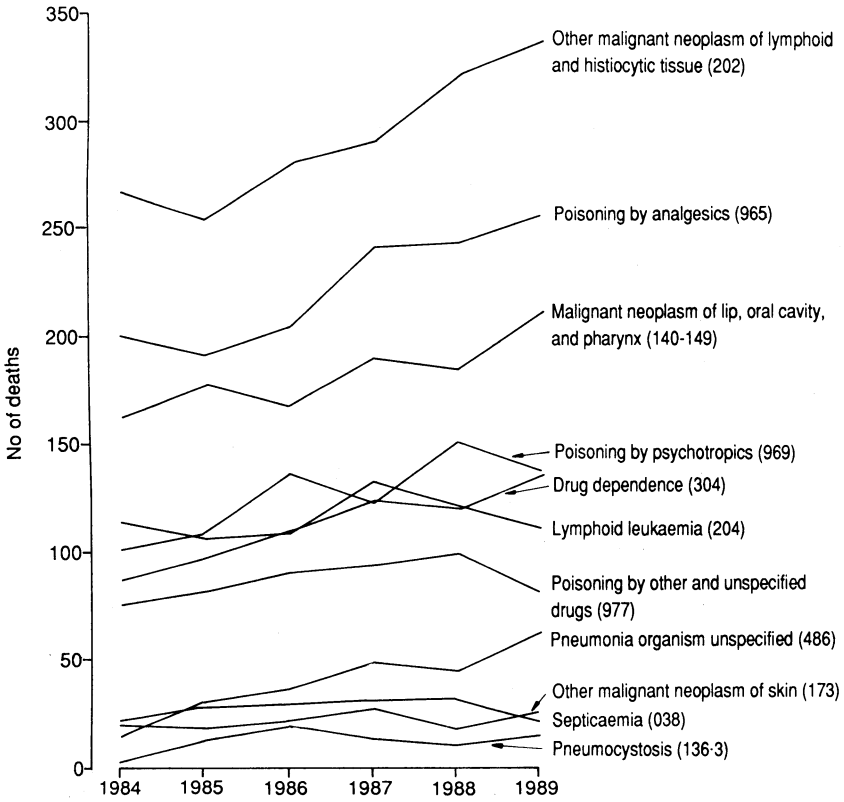
The figure shows the number of deaths in England and Wales in each year from 1984 to 1989 among men aged 15-54 due to the 11 selected causes. Table I presents the results of the inquiry into deaths due to medical and external causes. Of 271 replies received for medical causes, 37 were for men who were known to have been HIV positive, 31 of whom had been reported to CDSC; four were reported subsequently. Of 202 replies received for external causes, three were for men who were known to have been HIV positive. None had been reported to CDSC; two were reported subsequently.

Table II gives the number of deaths for which each cause was stated in 1989 and the number which would have been expected if the 1984 rates applied. The number of excess deaths is expressed as a proportion of the total number of deaths observed.

Table III gives the number of observed deaths and the estimated number of the expected excess deaths due to each cause in the six months of the study. Of the 101 estimated excess deaths, only 40 were in men known to have been HIV positive. The proportion of deaths in men with unrecognised HIV infection was 35% for medical causes, 93% for external causes, and 60% for all 11 causes.

Discussion

This study suggests that follow up of deaths for which conditions related to HIV are stated to be the cause is not an efficient way of increasing the number of cases reported to CDSC—only six additional cases were reported. The results suggest that only 40% of deaths among HIV positive men are in men known to be HIV positive by the time they die. This estimate is based on the assumption that the increase in the number of deaths due to these causes is associated with HIV infection. The age, sex, marital status, and geographic and temporal distribution all suggest that this is so for medical causes.[1] Although the evidence is less convincing for external causes, the number of men reported to CDSC who have died as the result of an overdose without developing an AIDS indicator



Number of deaths from selected HIV related causes (International Classification of Diseases codes) in men aged 15-54 in England and Wales

disease suggests that at least part of the increase is HIV related. This is supported by a report of the increased risk of suicide among people with AIDS in New York.[2]

The increasing number of reported deaths due to opportunistic diseases might result from improved diagnosis or immunosuppressive therapy. If this were so it would be expected that similar changes in death rates would be apparent among men of each marital state and among women. However, death rates from lymphoma (ICD 202) have increased among single men of all age groups from 15 to 44 years but show no similar increase among men of other marital states or among women. Death rates from pneumonia increased fourfold between the two three year periods 1984-6 and 1987-9 among single men aged 30-44 years and are 10 times those for other men and for women (unpublished data).

Men followed up in the study may have been known to be HIV positive but this information may not have been available to the person who replied to the inquiry. However, over 85% of people for whom AIDS or HIV infection is stated as the cause of death die in hospital, so any underreporting of positive tests to the patient's general practitioner is unlikely to have influenced these results. In addition, every man included in the follow up study who had been reported to CDSC was known by the respondent to be HIV positive.

In conclusion, the results have implications for the carers of people with these HIV related conditions. They also suggest that the full extent of the HIV epidemic has not yet been recognised. The study was, however, based on small numbers and further work needs to be done to verify the findings.

I thank all those clinicians and coroners who took so much trouble in replying to the inquiry letter.

1 McCormick A. Excess mortality associated with HIV epidemic in England and Wales. *BMJ* 1991;**302**:1375-6.
2 Marzuk PM, Tierney H, Tardiff K, Grass EM, Morgan EB, Hsu M-A, *et al.* Increased risk of suicide in persons with AIDS. *JAMA* 1988;**259**:1333-7.

(Accepted 18 April 1991)

Single dose cabergoline versus bromocriptine in inhibition of puerperal lactation: randomised, double blind, multicentre study

European Multicentre Study Group for Cabergoline in Lactation Inhibition

Abstract

***Objective*—To compare the efficacy and safety of a single dose of 1 mg of cabergoline with that of bromocriptine 2·5 mg twice daily for 14 days in the inhibition of puerperal lactation.**

***Design*—Prospective, randomised, double blind, parallel group, multicentre study.**

***Setting*—University or hospital departments of obstetrics and gynaecology in different European countries.**

***Subjects*—272 puerperal women not wishing to lactate (136 randomised to each drug).**

***Interventions*—Women randomised to cabergoline received two 0·5 mg tablets of cabergoline and one placebo tablet within 27 hours after delivery and then placebo twice daily for 14 days. Those randomised to bromocriptine received 2·5 mg of bromocriptine and two placebo tablets within 27 hours and then 2·5 mg of bromocriptine twice daily for 14 days.**

***Main outcome measures*—Success of treatment (complete or partial) according to milk secretion, breast engorgement, and breast pain; rebound symptomatology; serum prolactin concentrations; and number of adverse events.**

***Results*—Complete success was achieved in 106 of 136 women randomised to cabergoline and in 94 of 136 randomised to bromocriptine and partial success in 21 and 33 women respectively. Rebound breast symptomatology occurred respectively in five and 23 women with complete success up to day 15 ($p<0·0001$). Serum prolactin concentrations dropped considerably with both drugs from day 2 to day 15; a prolactin secretion rebound effect was observed in women treated with bromocriptine. Adverse events were reported by 22 women receiving cabergoline and 36 receiving bromocriptine ($p=0·054$), occurring mostly during the first treatment day.**

***Conclusion*—A single 1 mg dose of cabergoline is at least as effective as bromocriptine 2·5 mg twice daily for 14 days in preventing puerperal lactation. Because of the considerably lower rate of rebound breast activity and adverse events and the simpler administration schedule cabergoline should be the drug of choice for lactation inhibition.**

Report prepared by Professor R Rolland and Drs G Piscitelli, C Ferrari, and A Petroccione.

Members of the group are listed at the end of the paper.

Correspondence to: Professor R Rolland, Department of Obstetrics and Gynaecology, St Radboud University Hospital, 6500 H B Nijmegen, The Netherlands.

BMJ 1991;**302**:1367-71

Introduction

Despite the well known advantages of breast feeding, prevention or suppression of milk production may be indicated on medical or personal grounds.[1] Although tight binders may result in the suppression of puerperal lactation, appreciable breast pain and milk secretion frequently occur, especially in multiparous women.[2] Oestrogens given alone or in combination with