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ORIGINAL RESEARCH

Maternal mortality in rural South Africa: the impact of case definition on levels and trends

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Background: Uncertainty in the levels of global maternal mortality reflects data deficiencies, as well as differences in methods and definitions. This study presents levels and trends in maternal mortality in Agincourt, a rural subdistrict of South Africa, under long-term health and sociodemographic surveillance.

Methods: All deaths of women aged 15 years–49 years occurring in the study area between 1992 and 2010 were investigated, and causes of death were assessed by verbal autopsy. Two case definitions were used: "obstetrical" (direct) causes, defined as deaths caused by conditions listed under O00-O95 in *International Classification of Diseases-10*; and "pregnancy-related deaths", defined as any death occurring during the maternal risk period (pregnancy, delivery, 6 weeks postpartum), irrespective of cause.

Results: The case definition had a major impact on levels and trends in maternal mortality. The obstetric mortality ratio averaged 185 per 100,000 live births over the period (60 deaths), whereas the pregnancy-related mortality ratio averaged 423 per 100,000 live births (137 deaths). Results from both calculations increased over the period, with a peak around 2006, followed by a decline coincident with the national roll-out of Prevention of Mother-to-Child Transmission of HIV and antiretroviral treatment programs. Mortality increase from direct causes was mainly due to hypertension or sepsis. Mortality increase from other causes was primarily due to the rise in deaths from HIV/AIDS and pulmonary tuberculosis.

Conclusion: These trends underline the major fluctuations induced by emerging infectious diseases in South Africa, a country undergoing rapid and complex health transitions. Findings also pose questions about the most appropriate case definition for maternal mortality and emphasize the need for a consistent definition in order to better monitor and compare trends over time and across settings.

Keywords: maternal mortality, direct causes, pregnancy related deaths, Agincourt, South Africa

Introduction

Maternal mortality is a reflection of the state of public health and highly sensitive to targeted health interventions, both preventive and curative. For instance, in Sweden, maternal mortality was reduced 300-fold in two and a half centuries since 1750, because of better hygiene, better care, and innovative interventions during pregnancy, delivery, and the puerperium. Reducing maternal mortality by two thirds within 25 years (1990–2015) is the fifth "Millennium Development Goal" (MDG5a) set by the United Nations for low- and middle-income countries.[1–5]

Monitoring levels and trends in maternal mortality over a prolonged period was possible in European countries, because of comprehensive vital registration and cause

of death ascertainment; this is not the case in low- and middle income countries, particularly in sub-Saharan Africa. In fact, most estimates are from local studies (community-based or hospital-based), from demographic surveys (national census or sample surveys), or occasionally from "confidential enquiries". These sources have numerous biases and are rarely comparable because of varying population coverage and a lack of standard definition. The *International Classification of Diseases and Causes of Death, 10th revision* (ICD-10) distinguishes three categories: the "direct causes", which are obstetrical causes (listed under O00-O95 code); the so-called "indirect causes", which are due to selected infectious or noncommunicable causes assumed to be enhanced by the pregnancy (listed under O98-O99 code), and the "fortuitous causes", which are assumed to be independent of the pregnancy. All deaths that occurred during the maternal risk period (pregnancy, delivery, up to 42 days after delivery) are known as the "pregnancy related deaths". The situation was further complicated with the emergence of HIV/AIDS, now a major cause of death for women in their reproductive ages. The ICD-10 does not recommend including HIV/AIDS deaths among the indirect causes, but many analysts do, including the United Nations Maternal Mortality Estimation Inter-Agency Group.[6–12]

The case of South Africa is particularly interesting given the relatively extensive data on maternal mortality, the effects of the HIV/AIDS epidemic, and recent widespread introduction of Prevention of Mother-to-Child Transmission of HIV and antiretroviral therapy programs, and the apparent rapid increase in maternal mortality.[13] A critical question is whether the mortality increase is due to deterioration in the quality of obstetric care or to the complex effects of emerging diseases on pregnancy outcome. Several papers have addressed this issue.[14–24]

This article presents an empirical analysis of maternal mortality over some 18 years in rural South Africa. It highlights the critical importance of case definition for monitoring levels and trends in maternal mortality, and in particular for evaluating "safe motherhood" and MDG5a. The study also demonstrates the large fluctuations created by the HIV/AIDS epidemic on women's health.

Methods

The study was conducted in the Agincourt subdistrict of Mpumalanga Province, South Africa, adjacent to southern Mozambique, a rural setting under health and sociodemographic surveillance since 1992. The area covers a population of some 90,000 in 16,000 households, and was part of the

former Gazankulu Bantustan or "homeland", and is now in the Ehlangeni district. The district-based, nurse-led primary health care system includes a network of six clinics referring to a larger health center; three district hospitals are between 25 and 60 km away. Most deliveries occurred in the health facilities and antenatal care, and postnatal care is almost universal, although the quality of services is mixed. The Agincourt study has been described in detail elsewhere.[25–27]

The health and sociodemographic surveillance system (HDSS) covers the subdistrict and includes comprehensive monitoring of household composition and vital events: births, deaths, in- and out-migrations, and detailed verbal autopsies to establish likely cause of death. The system was introduced in 1992/1993 and has been updated annually since then. Data for this study cover the period to July 2010 and include 18 years of monitoring of vital events. Each year, well-trained fieldworkers visited every household in the study area, asked about vital events which had occurred since the last visit, and updated the household roster. In cases of death having occurred, a verbal autopsy was conducted with the closest caregiver of the deceased, by specially-trained lay fieldworkers, in order to establish signs and symptoms of the terminal illness, lifestyle risk factors, and treatments. The interview was conducted using a 25-page comprehensive questionnaire (available on request from the authors), which included open and closed questions, and was written both in English and Shangaan, the local language.[28] Completed questionnaires were independently reviewed by two physicians, who came to a consensus on the probable cause of death; a third physician assisted where the cause was disputed.[28] Death registration was considered nearly complete, and verbal autopsy diagnoses were validated by comparing them with causes of death determined at hospital.[29] The validation conducted in the early years, as well as more recently, indicated that all maternal deaths were correctly assessed by verbal autopsy, although the sample size was very small (six maternal deaths were compared with hospital diagnoses). Since the survey was conducted by interview with a close family member or community caregiver, there was no information on the HIV status of the deceased person. Mortality rates underwent major changes over the study period, with a marked increase between 1994 and 2006 due to the accelerating HIV/AIDS epidemic, and a decline since 2006 due to the extensive rollout and take-up of anti-retroviral therapy.[28,30–33]

All deaths of women aged 15 years–49 years that occurred among the resident population from 1992 to 2010 were investigated. Two definitions of maternal death were used: (1) "obstetrical" or "direct" causes (ICD10 code = O00 to O95)

(there were no late causes [O96-O97] in the sample); and (2) "any other cause" (indirect or fortuitous) that occurred during the maternal risk period. The total of (1) and (2) comprised all "pregnancy-related" deaths. We were not able to apply the World Health Organization's definition for "indirect" causes because of the difficulty in determining whether a mortality outcome was "aggravated by the physiologic effects of pregnancy". This is particularly important when appraising maternal deaths associated with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS). In a companion paper, we explain that mortality from infectious and parasitic diseases, or from noncommunicable diseases, was lower for pregnant women than nonpregnant women of the same age, so that no attributable risk could be assigned for indirect causes.[34]

There were missing values for the information on pregnancy (14%) and for causes of death (19%). Using an imputation method based on age at death, the possible undercount of the true number of maternal deaths was estimated at about 30% (32% for obstetric deaths, 28% for pregnancy-related deaths). However, for the sake of specificity, the analysis presented in this report was based only on the raw data, unadjusted for missing values.

Data were split into two periods: 1992/1993–2001 and 2002–2010. The first period corresponded to the end of the fertility transition (fertility decline) and the beginning of the HIV/AIDS epidemic. The second period was marked by the massive increase in mortality caused by a peak in the linked epidemics of HIV/AIDS and pulmonary tuberculosis, followed by the introduction of highly active antiretroviral therapy. Relative risks (RR) compared the second period (2002–2010) with the first period (1992–2001) considered as the baseline. Standard statistical tests of RR were computed using Excel 2010 (Microsoft Corporation, Redmond, WA, USA). The fitting of trends with polynomials was done using SPSS version16 (IBM Corporation, Armonk, NY, USA) linear logistic regression.

Results
Maternal mortality levels and trends
Since 1992/1993, the Agincourt study area hosted on average some 18,300 women aged 15 years–49 years. From the first to the second period (ie, 1992/1993–2001 to 2002–2010), the population increased by 19%, fertility declined by 19%, and mortality of women 15 years–49 increased 2.44- fold. Maternal mortality also doubled (RR = 2.08 for obstetrical causes, 95% confidence interval [CI] = 1.21–3.55; RR = 2.05 for pregnancy-related deaths, 95% CI = 1.44–2.93); whereas the proportion of direct causes remained low and declined somewhat, from 3.6% to 2.5%. Most differences between the two periods were highly significant (Table 1).

The maternal mortality ratio (MMR), expressed per 100,000 live births, was abnormally high and increasing.

Table 1 Maternal mortality data, Agincourt, South Africa 1992–2010

	Women 15–49 years	Period		RR	95% CI	Significance
		1992–2001	2002–2010			
Raw data	Person-years lived	150,091	178,757	1.19		
	Births	16,510	15,904	0.96		
	Deaths 15–49	555	1,615	2.91		
	Direct cause O00-O95	20	40	2.00		
	Pregnancy-related	46	91	1.98		
Rates	General fertility rate/1000	110	89	0.81	0.79–0.83	*
	Death rate/1000	3.70	9.03	2.44	2.22–2.69	*
	Percent direct	3.6	2.5	0.69	0.40–1.18	NS
	MMR (direct)/100,000	121	252	2.08	1.21–3.55	*
	MMR (Pregnancy-related)/100,000	279	572	2.05	1.44–2.93	*
Number of pregnancy-related deaths by cause (determined by verbal autopsy)						
Direct	Sepsis	2	9	4.67	1.01–21.6	*
	Hypertension	3	8	2.77	0.73–10.4	NS
	Other and ill defined	15	23	1.59	0.83–3.05	NS
Other	HIV/AIDS, TB	9	26	3.00	1.41–6.40	*
	Other infections	2	8	4.15	0.88–19.6	Borderline
	Noncommunicable	4	5	1.30	0.35–4.83	NS
	External	3	0	0.00		NS
	Unknown cause	8	12	1.56	0.64–3.81	NS
	Total	46	91	2.05	1.44–2.93	*

Notes: General fertility rate = births per 1,000 women age 15–49 per year; death rate = deaths per 1,000 women age 15–49 per year. *$P < 0.05$.
Abbreviations: CI, confidence interval; MMR, maternal mortality ratio (per 100,000 live births); NS, not significant; RR, relative risks; TB, tuberculosis.

For obstetrical causes, MMR increased from 121 to 252 per 100,000. For pregnancy-related deaths, MMR increased from 279 to 572 per 100,000. While a very high value, this appears consistent with national estimates from the 2001 census and 2007 community survey (542 and 702 per 100,000, respectively).[14–17]

Trends in maternal mortality were not linear. As with general mortality, maternal death rates first decreased over time then increased to a peak around 2006 before decreasing again. The changing rates were fitted with a third degree polynomial on individual data. The peak of obstetrical mortality could be as high as 300 per 100,000, and that of pregnancy-related mortality as high as 670 per 100,000 births, and potentially higher if missing values were included (Figure 1).

Causes of death

Despite the small number of cases, there was a pattern of change in the cause of death structure. For obstetrical causes, 60% of the increase (12/20 deaths) was due to postpartum infections (RR = 4.67) and hypertensive causes (eclampsia/pre-eclampsia: RR = 2.77). The increase in mortality from other causes (RR = 1.59) such as hemorrhage, obstructed labor, ectopic pregnancy, abortion, or obstetrically related pulmonary embolism was not statistically significant (Table 1).

Examining other causes (indirect and fortuitous) indicated that 92% of the increase (23/25 deaths) was due to HIV/AIDS, pulmonary tuberculosis, and other infections. In contrast, the contribution of deaths from noncommunicable diseases and external causes changed little (15 and 17 deaths respectively). Among the other infectious and parasitic causes, many were probably related to HIV/AIDS, notably septicemia (one case), meningitis (four cases), and pneumonia (one case); the remaining four cases were malaria deaths. Two-thirds of noncommunicable causes were cardiovascular diseases, the remainder were due to cancer of the female genital tract, asthma, and liver disease. The number of undetermined causes also increased but not in proportion to all deaths (17.4% and 13.2%, respectively).

Comparison with the confidential enquiries

The comparison with the confidential enquiries conducted since 1998 was difficult to perform. Firstly, the level of maternal mortality was different, since the confidential enquiries into maternal deaths (CEMD) recorded only maternal deaths in facilities with information on pregnancy. For instance, for the 2008–2010 period, the MMR for pregnancy-related deaths in the CEMD was 180 per 100,000 in South Africa as a whole, and 174 per 100,000 in the Ehlanzeni district (where Agincourt is situated), whereas the HDSS recorded 603 per 100,000 during the same period (raw data) and 780 per 100,000 after correction for missing values. The CEMD records, therefore, accounted only for about a quarter of the pregnancy related deaths, which could lead to a selection bias. The CEMD indicated a steady
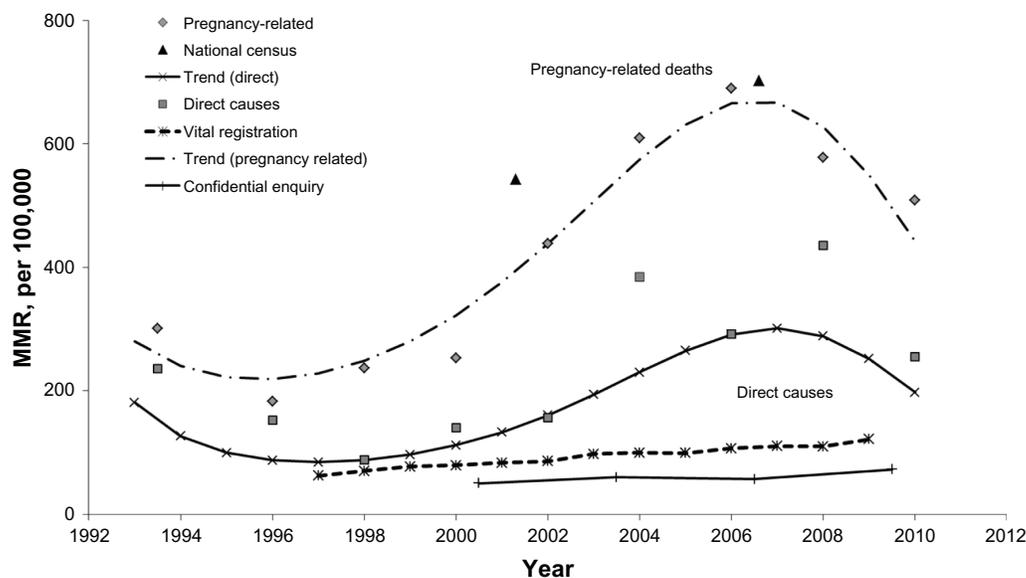

Figure 1 Trends in maternal mortality, Agincourt, subdistrict, South Africa 1992–2010.
Notes: National censuses were conducted in 2001 and 2007; census data apply to the 12 months before census. Vital registration data and confidential enquiries from published statistics (direct causes only).
Abbreviation: MMR, maternal mortality ratio.

increase in MMR over the years, both for pregnancy related deaths and for direct causes, probably because of increasing coverage over time, whereas Agincourt indicated ups and downs. The proportion of direct causes was essentially the same in the CEMD (48%) and in Agincourt (44%), and the small difference could be explained by the inclusion of external causes in Agincourt. The leading causes were also basically the same in Agicourt and in the CEMD, although the breakdown of the classification was not identical: the CEMD did not distinguish "obstructed labor", whereas Agincourt does not have any category for "anesthetic related", or "acute collapse". Furthermore, in Agincourt, the coding of causes in the most recent period was not strictly identical to that done in earlier periods for hemorrhage. In terms of mortality increase, the trends were difficult to compare because Agincourt included a pre-AIDS baseline period (1992–2001), whereas the baseline for CEMD (1998–2001) was after the increase in AIDS mortality. In Agincourt, mortality doubled from 1992–2001 to 2002–2010, whereas it increased only by 26% in the CEMD from 1999–2001 to 2002–2010. The strong increase in Agincourt for hypertensive disorders (RR = 2.77) and for sepsis (RR = 4.67) was larger than in the CEMD (RR = 1.20 and 1.15, respectively). The strong increase in hemorrhage in the CEMD (RR = 1.51) could not be verified in Agincourt because of coding inaccuracy after 2002. Only one category had a similar trend: ectopic pregnancy, miscarriage, and abortion increased similarly in Agicourt (RR = 1.30) and in the CEMD (RR = 1.32).

Discussion

The level of maternal mortality sustained in the Agincourt subdistrict was surprisingly high for a middle-income country like South Africa, as has been noted at national level.[14] The level of obstetrical mortality documented corresponded to that of Sweden around 1900;[1] while the level of pregnancy-related deaths matched the highest levels recorded in African Demographic and Health Surveys.[35] This occurred despite the relatively small proportion of deaths due to maternal causes in women 15 years–49 years, a fraction much lower than in comparable situations elsewhere.[35] This is a new pattern which deserves further attention and has implications for mathematical models based on these proportions.

The Agincourt HDSS data include all maternal deaths that occurred in the study area population over the study period, irrespective of the place of death. They include deaths that occurred at home, in hospitals, en route for care, or elsewhere, and therefore the rates obtained from the demographic surveillance differ from those obtained by

other methods, in particular from the confidential enquiries. Agincourt estimates also differ from the vital registration estimates, especially for pregnancy-related deaths. This is mainly due to the fact that the information on pregnancy is completed in only a small proportion of deaths of women age 15 years–49 years (only 28% in the vital registration data for 2006–2009). Improving the coverage of the vital registration system, as well as improving the entry of system forms, is crucial for rigorously monitoring the rapidly changing levels of maternal mortality. Studies such as the Agincourt HDSS contribute to understanding the weaknesses of current health information systems in South Africa.

The magnitude and speed of the changes in maternal mortality in Agincourt was outstanding. The first period (up to 1996) follows a standard pattern of mortality decline found in countries undergoing a health transition; the second period (1996–2006) witnessed a three-fold increase in about 10 years, which is unique in the world; the speed of the decline after 2006 seems to be as rapid and as important. These changes appear to be a direct consequence of the dynamics of the HIV/AIDS epidemic, and seem unrelated to the quality of obstetric care. The magnitude of the changes makes it impossible to have a single estimate of MMR, and explains in part the confusion that arose about national estimates of MMR.

Trends in maternal mortality did not decline as might be expected given South Africa's stated commitment to the MDG5a and the relatively high access to, and quality of, maternal health services. This disappointing pattern seems driven to a large extent by high levels of HIV/AIDS and tuberculosis. Arguably, the trends observed in MMR are no longer an indicator of safe motherhood, but simply a marker of the dynamics of evolving infectious disease epidemics.

The case definition was important in characterizing the level of maternal mortality. In fact, a lack of standardization can produce confusing estimates that range from 91 to 820 per 100,000 at national level based on the same data but applying different case definitions and statistical methods.[14] Our study underlines the need to better characterize "obstetrical causes," and to adhere to a strict and consistent definition in order to monitor and compare trends over time and across different settings.

The basic structure of causes of maternal death observed in Agincourt, which include deaths in the community as well as in health facilities, does not seem to differ from that found in other sources in South Africa, although precise comparisons are difficult due to a lack of standardization and different data sources. Compared with the confidential enquiries into maternal

mortality, limited to health facility-deaths, the proportions and ranking of major causes were comparable for hypertensive disorders, hemorrhage, puerperal sepsis, abortion, and ectopic pregnancy.[36] However, the proportion attributed to puerperal sepsis could be inflated in Agincourt by the inclusion of other infectious diseases related to HIV/AIDS, and this may explain why the increased mortality from these causes appeared more pronounced in Agincourt than in national data.

The indirect role of HIV/AIDS on the obstetrical causes needs further analysis. Since many of the classic obstetrical causes did not change over the years, one could attribute most of the change (infections and hypertension) to the direct and indirect effects of HIV/AIDS. Some of the increase in miscarriage and abortion could also be due to HIV/AIDS. The inclusion of some AIDS deaths among the deaths due to puerperal infection may be a diagnostic problem when coding causes of death in verbal autopsies. There is a need to examine this category by specific infectious cause, which remains difficult because of the small number of cases and lack of precision of verbal autopsies.

The increase in hypertensive disorders, also found in the confidential enquiries and in vital registration system data, deserves further research. While not due to HIV infection directly, this could be attributed to its treatment. Indeed, recent studies reported that highly active antiretroviral therapy could induce hypertension and potentially increase maternal mortality from pre-eclampsia and eclampsia. Active antiretroviral therapy may also have an effect on mortality from liver disease.[37,38]

In the context of a severe HIV epidemic such as that in Southern Africa, levels and trends in maternal mortality, even when restricted to obstetrical causes, no longer appear to be the exclusive indicators of the quality of obstetric care. This perspective is critical when monitoring change and trends in MDG5a and interpreting their significance for policy and programs relating to sexual and reproductive health and safe motherhood.

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Author contributions

All authors contributed significantly to the paper, agreed with the analysis and approved the final version. MG did the statistical analysis and wrote the first draft. KK was responsible for establishing the verbal autopsy (VA) system and the ongoing assessment of VA questionnaires; she contributed to the writing of the manuscript. MC was responsible for the fieldwork until 2005, contributed to the interpretation of data, made changes on the first draft, and contributed again to the final draft. FXGO was responsible for the fieldwork, a key person in the data collection since 2005 including registration of all deaths and implementation of the verbal autopsy, made changes on the first draft, and contributed again to the final draft. ST was director of the entire project and contributed to conceptualizing the work and writing the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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