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Where the Burden Lies: A framework and evaluation of systematic error in measurement of the health effects of unsafe abortion

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Where the Burden Lies: A framework and evaluation of systematic error in measurement of the health effects of unsafe abortion

By

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University of California, Berkeley

Committee in charge:
Professor Jennifer Ahern, Chair
Professor Malcolm Potts
Professor Steven Selvin
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Abstract

Where the Burden Lies: A framework and evaluation of systematic error in measurement of the health effects of unsafe abortion

By

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Background:

Measuring the incidence and sequellae of unsafe abortion is notoriously challenging. In the parts of the world where abortion is considered unsafe, it is often also illegal (or heavily restricted), and highly stigmatized. Women experiencing abortion related complications, for fear of severe legal, social, or religious repercussions, are, therefore, less likely than women experiencing other kinds of pregnancy-related complications to seek care in medical facilities, or disclose their experiences with abortion.

Biases are repeatedly discussed in accounts of post abortion care (PAC) [2] [3,4] where researchers are interested in the proportion of cases resulting from induced vs. spontaneous abortion, often in similarly restrictive legal and social settings. Classification of PAC resulting from induced abortion as PAC resulting from spontaneous abortion is known to occur frequently, and the reverse is also thought to be common.

The field of global reproductive health needs a simple, straightforward, quantitative framework through which to assess the expected direction and magnitude of biases that exists in studies of unsafe abortion (and resulting sequellea). Such a framework would not only allow the researchers to better quantify bias in their own studies, but would aid readers ability to incorporate quantitative information about existing biases into their interpretation of results.

Methods:

Analyses investigating separate research aims related to systematic error in the measurement of unsafe abortion related mortality and morbidity will be conducted over three chapters, as follows: Chapter 1: Systematic Review of current estimates of unsafe abortion related mortality from 2000-2011, Chapter 2: Bias Framework and Multiple bias analysis of the proportion of maternal mortality resulting from unsafe abortion, and Chapter 3: Multiple bias analysis of unsafe abortion related post abortion care seekers in Zanzibar, Tanzania.

Discussion and Significance:

The results of the three preceding analyses suggest it is likely that unsafe abortion has been significantly underestimated as a cause of maternal death and post abortion care. These results have clear implications for increasing efforts aimed at the proven interventions which help to decrease abortion related mortality and morbidity: reducing unintended pregnancy, ensuring access to safe abortion services where it is legal, increasing access to safe abortion services where laws have the potential to be revised, and providing access to comprehensive post abortion care with contraceptive counseling in places where access to abortion remains highly restricted. These results also have implications for scientists committed to producing sound evidence in a field with endemic measurement challenges. Improving methods to quantify the direction and magnitude of systematic error in studies, and integrate such information into the interpretation of results concerning the burden of unsafe abortion-related mortality and morbidity is the necessary first step in understanding these grave public health concerns, and targeting interventions that appropriately address their underlying causes.

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Dedication

To my husband, Joshua Gruber, who, with a simple drawing on the back of a cocktail napkin, was the first to inspire my love epidemiologic methods ithout fervid unrelenting, efforts to make me a better epidemiologist, this dissertation would not exist.

And to my dearest friends and family (you know who you are): your enduring love and support made all of this possible in the first place.

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INTRODUCTION

Measuring the incidence and sequellae of unsafe abortion is notoriously challenging. In the parts of the world where abortion is considered unsafe, it is often also illegal (or heavily restricted), and highly stigmatized. Women experiencing abortion related complications, for fear of severe legal, social, or religious repercussions, are, therefore, less likely than women experiencing other kinds of pregnancy-related complications to seek care in medical facilities, or disclose their experiences with abortion.

In 2006, the WHO published the fifth update of an ongoing report documenting the global incidence and trends of unsafe abortion. The authors conducted a rigorous analysis of all available data on mortality from unsafe abortion, and, to the best of their ability, calculated the global and regional incidence of unsafe abortion. Because of the often sparse, poor quality data in countries where abortion is the least safe, however, the authors state that "*…because of the level of uncertainty, estimates of the incidence of unsafe abortion and the resulting mortality…should be considered only as best estimates given the information currently available. It is likely that the true incidence of unsafe abortion and the related mortality rate are higher than estimated* (pg. 13-14) [1] ."

Biases are repeatedly discussed in accounts of post abortion care (PAC) [2] [3,4] where researchers are interested in the proportion of cases resulting from induced vs. spontaneous abortion, often in similarly restrictive legal and social settings. Classification of PAC resulting from induced abortion as PAC resulting from spontaneous abortion is known to occur frequently, and the reverse is also thought to be common.

Given the known limitations to the measurement of unsafe abortion, and its related mortality and morbidity, coupled with researchers' acknowledgement of the limitations of their data, the often brief, qualitative discussion of bias offered in the limitations sections of academic papers leaves readers asking more questions than are answered.

The field of global reproductive health needs a simple, straightforward, quantitative framework through which to assess the expected direction and magnitude of biases that exists in studies of unsafe abortion (and resulting sequellea). Such a framework would not only allow the researchers to better quantify bias in their own studies, but would aid readers ability to incorporate quantitative information about existing biases into their interpretation of results.

Drawing from the epidemiologic literature, just such a framework emerges. Epidemiologists are trained to assess two kinds of error in studies: random error (the precision of estimates) and systematic error (the validity of estimates). A clear consensus has been reached, across scientific fields, regarding the quantitative reporting of random error; the ubiquitous 95% confidence interval. Less common, but becoming more so, is the use of quantitative bias analysis to evaluate and report systematic error.

Bias analyses employ mathematical techniques to compare observed study data to the counterfactually true data had no bias existed [5]. Employing the epidemiologic construct of systematic error, an author must first determine which biases (confounding bias, information bias, and selection bias) are likely to exist in her study. Then, using expert knowledge, and data from validation studies (where they exist), she must construct parameters (or distributions) of the probable magnitude of those biases. Finally, after applying the distributions ("bias parameters") to her data, the author can randomly sample from those parameters, many thousands of times (much like a bootstrap) to "adjust" for the existing biases and generate hypothetical distributions of her point estimate had no bias existed in her study at all[6].

Indeed, bias analysis techniques are not without critics. Some argue that the results of such analyses are themselves biased by the values chosen by the author for each bias parameter. There is no disputing that the parameters chosen, by their nature, dictate the results of bias analyses. However, by virtue of making a priori statements of the presumed biases and their supposed magnitude in a study, an author establishes a clear, transparent process by which systematic error was assessed. That process can be followed by readers, who can make their own assessments about the correctness or incorrectness of the authors bias parameters, and how results would change if the parameters had been different. This method is a vast improvement on the traditional, qualitative discussion of potential bias, in which no attempt is made to quantify known sources of systematic error, or to correct for such error.

The ability to better quantify the range of potential values for the burden of abortion related sequellea in countries where abortion is considered unsafe, has clear implications for health systems, family planning programs, and interventions targeted at the reduction of maternal mortality and morbidity. Bias analysis techniques that generate simulation intervals (ranges of possible values under bias corrected scenarios) for these sequellea allow scientists in the field and decision makers alike the ability to better interpret the full range of the possible impact of policies and programs targeting these outcomes.

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Chapter 1

Measuring Unsafe Abortion Related Mortality: A Systematic Review of the Existing Methods

Background

The true global burden of unsafe abortion-related mortality remains unknown. Employing the newest figures for global maternal mortality, the WHO estimates that in 2008 approximately 13% of maternal mortality worldwide, or 47,000 deaths were due to unsafe abortion.[1] Such estimates, however, are based on statistics from developing countries that are known to have unreliable data,[2] and are, at best, thought to underestimate the true global incidence of mortality from unsafe abortion. [2-4]

Maternal deaths occur most often in settings where national vital registration systems are weak or non-existent.[2, 3] As such, measurement of maternal mortality relies on alternative methods of data collection; [5] estimates of all-cause maternal mortality can be derived from population-level surveys [6] or indirect estimation techniques.[7] Some recent methodological advances have been made in measurement techniques for all-cause maternal mortality,[7, 8] an issue that has received increased attention since the inclusion of a commitment to reductions in maternal mortality (reducing maternal mortality by 75% from 1990 levels by the year 2015) as a part of the Millennium Development Goals (MDGs) in the year 2000. Such improvements in the measurement of abortion related deaths, however, have been slow to develop.[9]

Cause-specific maternal mortality data, where cause of death is identified as one of the WHO specified direct or indirect obstetric causes of death, [10] can be captured through vital registration (death certificates), hospital or facility records (case notes and/or death certificates), verbal autopsy (a WHO validated tool for measuring cause-specific mortality at the community level through a structured questionnaire with family members of a recently deceased person, to assign cause of death (COD) in the absence of vital registration data),[11, 12] or Reproductive Age Mortality Studies (RAMOS), which combine vital registration data and verbal autopsy data.[13] Abortion-related mortality, a direct obstetric cause, is uniquely difficult to document for a number of reasons: 1) In countries where abortion is restricted or illegal altogether, women often seek abortion related services outside of the formal medical system; 2) In such settings, due to social and cultural stigma, and fear of legal consequences, women are often reluctant to seek medical services in the event of complications or reveal to family members the underlying cause of the complications;[14-21] 3) Because of legal consequences for patients and providers alike, clinicians who provide abortion-related services may be reluctant to report abortion-related deaths.[9, 15, 22]

The validity of existing estimates of unsafe abortion-related maternal mortality has been called into question,[3, 4] and the consequences of continuing to ignore measurement deficiencies in this field have real implications for the development of policy and implementation of programs that aim to reduce maternal mortality. However, to date there has been no assessment of the validity of existing studies that report estimates of the burden of abortion-related mortality with respect to the biases they may suffer from.

Our aim is to systematically review the available peer-reviewed evidence on unsafe abortion-related mortality published since the establishment of the MDGs (September, 2000). This review establishes criteria for evaluating the quality of research papers that cite estimates of abortion-related mortality, and presents a discussion of the methodological strengths and weaknesses of the current peer-reviewed evidence about abortion-related mortality.

Materials and Methods:

Search Strategy

We followed a protocol adapted for the evaluation of observational studies from criteria established by the PRISMA statement[23]. Pubmed, Popline, Embase, Medline, and JStor were searched for English-language studies published between September 1st, 2000 and December 1st, 2011. Combinations of the following keywords were used in the search process: *abortion, induced abortion, unsafe abortion, maternal mortality, maternal death, pregnancy related death, cause of death, verbal autopsy*. Reference lists of relevant articles were reviewed for sources that may have been missed in the database search. The full, line-by-line search strategy for each database can be found in Appendix 1.

Inclusion and Exclusion Criteria

To be included, articles had to meet the following criteria: (1) published after September 1st, 2000 and before December 1st, 2011; (2) conducted in or use data from a country where abortion is "considered unsafe"; (3) enumerated causes of maternal death, and specified "abortion" as one of those causes; (4) enumerated at least 100 maternal deaths from all causes; (5) a quantitative research study; (6) published in a peer-reviewed journal. The justification for each criterion is elaborated below.

We established calendar date restrictions for the search strategy (**Inclusion Criterion # 1**) to examine evidence published since the establishment of the Millenium Development Goals (MDGs). The MDGs set a specific target for the reduction of maternal mortality by 75% from 1990 levels by the year 2015, sparking interest in improved measurement of maternal mortality and an infusion of new funds for maternal mortality research.

Included studies were restricted to countries where abortion is "considered unsafe" **(Inclusion Criterion #2)**, using criteria developed by Adler *et al* [24]. While no international standard exists for the classification of such countries, Adler *et al* excluded regions of the world where the WHO classifies the incidence of unsafe abortion and associated deaths as "negligible".[1] We followed the same classification system, resulting in the exclusion of studies from the AMRO A (Canada, Cuba, United States), EURO A (Andorra, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom), and WPRO A (Australia, Brunei Darussalam, Japan, New Zealand, Singapore) regions. Studies conducted in all other regions of the world were considered for inclusion.

We included studies that enumerated the direct obstetric causes of maternal death in a study population (**Inclusion Criterion #3**), specified the cause "abortion", and calculated the number and or proportion of maternal deaths that were due to abortion. Because the definition of abortion varies widely in the literature, various definitions were accepted including: clinical definitions of induced abortion and/or unsafe abortion; all definitions of induced abortion provided by the International Classification of Disease (Code #'s 632, 635-639, and 640.03).[10] There is compelling evidence to suggest that in low-resource settings, it is often difficult to distinguish between induced abortions spontaneous abortions, therefore, in much of the

literature, abortion is defined as a combination of both the ICD definition of induced abortion (see above for code #'s) and the ICD definition of spontaneous abortion (ICD Code # 634)[16, 25]. Given that this is an internationally accepted definition of abortion, definitions that combined induced and spontaneous abortion into one category were also accepted. Deaths from spontaneous abortion as an independent category were not included.

The sample size criterion (**Inclusion Criterion #4**) was established to ensure sufficient sample size for adequate precision of estimates of abortion related deaths and was based on the sample size calculations from past reviews of abortion-related sequelea. [24, 26]

We aimed to evaluate the current, quantitative evidence on the burden of abortion-related mortality. To that end, articles that did not consist of original, quantitative research **(Inclusion Criteria #5)** such as review articles, commentaries, opinion pieces, and case studies, were not included.

Finally, because this review is focused on evaluating the highest quality evidence available, only articles that had first undergone a peer-review process were eligible for inclusion (**Inclusion Criteria #6**).

Rating Criteria

Studies were evaluated for quality on a scale modeled after a rubric developed by Charles et al[26] and derived from five primary criteria: 1) study design; 2) diagnostic procedures for assigning cause of death; 3) definition of abortion; 4) study reporting; 5) risk of bias (Table 1). Studies were ranked on the scale from Excellent to Very Poor. Table 2 provides the rubric for study evaluation.

Methodological Considerations for Development of Evaluation Rubric

I. Sources of Mortality Data

Nearly two-thirds of the worlds' countries do not routinely register vital events and thus lack complete information about births and deaths.[6, 27] Maternal mortality is often more difficult to measure than other deaths due to unique challenges in identifying and classifying maternal deaths, and especially abortion-related deaths.[6, 8] Facility-based maternal deaths are often not classified as maternal deaths if women were not registered in the labor and delivery wards (for example, the death occurred in the emergency department), and can be missed if women are not identified as pregnant, which is more likely in case of abortion-related deaths because the there may not be evidence of the pregnancy, or because of reporting errors due to legal concerns about treating patients with abortion related complications. [2, 4, 28] Despite the incomplete nature of the data, maternal mortality data in low-income countries can be extracted from numerous sources including medical-facility records, vital registries (when available), coroners' records, churches, and community registries. For community-based studies to gather the most complete possible count of maternal deaths, multiple sources of data (facility records, and community-based sources) must be reviewed to identify of maternal deaths.[28, 29] For facility-based studies, records from multiple departments or wards must be reviewed to ensure comprehensive capture of maternal deaths in the facilities.[28, 29]

II. Study Protocol

Variations in protocol used to assign cause of death for maternal deaths are common, and the quality of data sources vary with regard to the quality of information available for cause of death assignment.[29] Nevertheless, standard clinical definitions of direct and indirect causes of maternal death exist, and international guidelines are provided by the International Classification of Disease.[10] Studies should provide a standardized definition of causes of maternal death, and should follow clinical or international standard protocol for cause of death attribution. Verbal autopsy studies must contend with an additional layer of complexity due to the non-clinical nature of the data collection process. Various algorithms based on ICD-10 definitions have been developed for clinicians and computer-based algorithms to assign cause of death from verbal autopsy data with the highest degree of validity possible. [30] While computer-based algorithms for cause of death assignment have been validated in facility-based settings,[31, 32] the generalizability of such algorithms, derived from cause of death distributions in facilities, may be limited in community settings.[33] Studies that assign cause of death from verbal autopsy data should establish the procedure used and should justify the choice of algorithm based on the study sample.

III. Selection Bias

When the aim of a study is to document the total and cause specific burden of maternal mortality for a general population (e.g. a city, a country), facility based studies may suffer from selection bias because women with abortion related complications face a range of barriers to the access of medical services, including regulations that restrict access to safe abortion, cultural practices that stigmatize abortion, and socio-economic conditions that often lead women to attempt unsafe abortion even in settings where abortion is safely available. Facility-based data from developing countries where access to health facilities may be limited by social, cultural, and economic factors, are rarely generalizable to populations outside of those seeking medical care in facilities. Nevertheless, studies often attempt to make inference from facility-based data to a larger target population (e.g., surrounding communities). Such interpretations compromise the internal validity of facility-based studies.

The obstacles to medical care for women who have abortions outside of the formal medical system may produce underestimates of abortion-related mortality in facility-based datasets. In some circumstances, selection bias could also cause over-estimation of abortion-related mortality; in facility-based studies that use datasets collected from referral hospitals, abortion-related deaths may be over-represented as a proportion of maternal deaths. This is because a) the most severe cases may get sent directly to referral hospitals and b) delays in seeking care may disproportionately affect women with abortion-related complications resulting in those cases arriving at referral facilities too late to save the women's lives. [25]

IV. Misclassification

Some women who experience complications from an unsafe abortion will seek care in health facilities; however, even among those who do, in settings where abortion is legally restricted or culturally stigmatized, women are often reluctant to disclose attempted abortion to providers. Such underreporting of abortion-related complications in facilities is a form of misclassification that almost surely leads to an underestimate of abortion related deaths.[3, 9] Verbal autopsy may provide some advantages over facility-based estimates in providing estimates of abortion related death at the community level, but the stigmatization of abortion often influences what

information is reported by relatives, and may lead to misclassification. Mortality resulting from unsafe abortion is often a highly stigmatized event[14, 34] and the social, economic, and legal considerations surrounding abortion may lead to a reluctance among family members report abortion-related deaths. [20, 21]

Women who experience complications from unsafe abortion most often present to facilities with symptoms much akin to hemorrhage or sepsis. Physicians who assign cause of death may unintentionally misclassify abortion related deaths as death from hemorrhage, sepsis, or spontaneous abortion.[5, 20, 25] The risk of misclassification is heightened with verbal autopsy data, as physicians do not have the advantage of examining a patient and must rely on the accuracy of symptoms and contributing factors reported by non-clinicians.[35-37] Additionally, in settings where abortion is legally restricted, providers can face legal action if they provide medical care to a patient who has attempted to induce abortion.[9] Thus, in an effort to provide much needed care for their patients, providers may intentionally misclassify abortion-related complications and deaths, leading to differential misclassification that is almost certain to produce an underestimate of abortion related deaths.[37] Finally, when cause of death is unclear, it can be assigned as 'unknown cause', and evidence suggests that, because of its unique measurement challenges, abortion related death is more likely than the other obstetric causes to be classified as 'unknown'.[37, 38]

All studies were evaluated with respect to the degree to which they achieved the five criteria outlined in Table 1. Emphasis was placed on the potential of study results to suffer from the various bias considerations outlined above, and the extent to which authors addressed these biases in analysis or interpretation of their findings. In addition, 10 studies were selected randomly and were reviewed by a second reviewer (DV) to determine inter-rater reliability. All studies were evaluated using the same rubric and with particular attention to the methodological considerations outlined above.

Results

Figure 1 summarizes the results of the search process. The initial search strategy identified 7,438 articles. After excluding all duplicate titles, and reviewing titles and abstracts for English language and relevance to the research question, the full text of 92 articles were reviewed for possible inclusion in the study. Of those articles whose full text was reviewed, 56 did not meet inclusion criteria. Two articles were review articles, synthesizing data from a variety of sources, forty-five articles did not meet the sample size inclusion criteria, five articles were not published in peer-reviewed journals, and three articles did not report any abortion related deaths in their sample. The total number of studies included in the review was thirty-six.

The thirty-six articles included in this review were conducted in a wide range of settings; the majority were conducted in Sub-Saharan Africa (n=18), nearly one third of studies were conducted in Asia (n=10), while four studies were conducted in Latin America and the Caribbean, and another four studies conducted in the Middle East. The articles can be divided into two types of studies: 1) *facility-based studies* (n=22) where all data were collected at hospitals or medical facilities, and 2) *community-based studies* (n=14) where data were collected from a variety of data sources in the community. Of the community-based studies, some included data from facilities (n=8). A variety of study designs were used, not all of which conform to traditional epidemiologic designs. However, of thirty-six included studies, twenty three retrospective designs, three were ambi-directional designs, and ten were prospective

designs. Sample sizes of the included studies ranged from 104-769 maternal deaths. Twenty-two out of thirty-six (61.1%) studies provided a clinical or international standard definition of abortion. No study presented confidence intervals, or any measure of precision for estimates of abortion-related mortality or any other cause of mortality. Table 3 summarizes the main findings of each of the studies reviewed by quality rating.

Quality Rating:

No study received a rating of *Excellent*; this can primarily be attributed to poor evaluation for the criterion "Risk of bias". To be considered "Excellent", studies would have had to empirically demonstrate (through validation studies or other methods) that their data were free from major sources of systematic error, or, in the absence of such freedom from bias, perform a quantitative analysis of the effect of potential biases present in the data (through sensitivity analyses or other bias correcting techniques). No study attempted either strategy.

Of the 10 randomly selected studies that were reviewed by two raters (DV and CG), all ten were assigned to the same rating categories by both raters. Although the exact ranking varied slightly across reviewers, the categories of quality ratings were assigned consistently.

Meta-analysis of the data from the thirty-six studies was determined to be inappropriate due to the wide variation in context, study design, and measures. Findings, however, were qualitatively analyzed to determine whether any discernable pattern emerged by quality, geographic region, or type of study with regard to the proportion of abortion-related deaths reported by each study. Overall, studies receiving a "Very Good" rating found the highest estimates of abortion related mortality (median: 16%, range 1-27.4%). Studies receiving a "Very Poor" rating found the lowest overall proportion of abortion related deaths (median: 2%, range 1.3-9.4%). Table 4 shows the studies by quality level and proportion of abortion related deaths reported.

Ten of thirty-six studies received the rating of *Very Good*. All studies in the *Very Good* category used multiple data sources to identify maternal deaths, provided the international standard definition of abortion (ICD version 9 or 10), and clearly described the methods used to assign cause of death. Predominantly, studies that were categorized as *Very Good* were prospective in design. Despite the lack of quantitative bias assessment, all studies receiving a *Very Good* rating enumerated the biases thought to be present in their data, and provided a thorough discussion of potential study limitations and cautions to be taken in interpreting the results of the studies. The 2001 paper by Sloan, *et al* [39] provides a notable example of such a discussion. In this paper, the authors reanalyzed data from a verbal autopsy study conducted in three regions of rural Mexico in 1995, using multiple validated methods to determine cause of death from verbal autopsy. The paper aimed to assess variations of cause of death found through the various methods used. In their discussion, the authors discuss various limitations of verbal autopsy data, stating that

"In our rural study, many women delivered at home and the information given on death certificates was probably both incomplete and inaccurate, rarely being based on pathological examination or direct observation…".

Additionally, the authors note that variations in the distribution of cause of death using different methods for assigning cause of death were at times so great that the data became un-interpretable.

Six out of thirty-six studies received a *Fair* rating. Studies in the *Fair* category varied in the sources of data reviewed; some reviewed multiple sources of data, others reviewed only hospital records. A mix of retrospective, prospective, and ambi-directional study designs were used. All studies, however, provided a definition of abortion, and most reported with sufficient detail the procedures used to assign cause of death. No study that received a *Fair* rating provided a detailed description of limitations or the potential for biases contained in the data. One typical "Fair" study is a nationally representative cohort study of maternal deaths in Egypt, conducted by Campbell, et al in 2005. This study reviewed official records of maternal deaths, collected through active surveillance of maternal deaths during two one-year periods (1992-1993, and the year 2000) and followed up with verbal autopsy to assign cause of death. Clear definitions of maternal death and all cause of death were provided based on international standards, and the citation for ICD-10 classification of cause of death was provided. A detailed description of physician training in verbal autopsy and cause of death assignment was given, and the procedure for validation of cause of death (repeating verbal autopsies in a percentage of cases to ensure validity of initial recording) was clearly articulated. Despite the large sample size (772 maternal deaths in the first year, 585 in the second year) and the nationally representative nature of the data, the authors provide no discussion of the general limitations of verbal autopsy for assigning cause of death nor do they provide any assessment of potential misclassification or underreporting that could have occurred with respect to abortion related deaths because of the legal status or stigma surrounding abortion.

Fourteen of thirty-six studies received a rating of *Poor*. These studies predominantly used retrospective study designs, most were facility-based studies, and no studies categorized as *Poor* used multiple sources of data to identify maternal deaths. Only three studies in this category provided a definition of abortion (two studies reported clinical definitions, one study reported ICD-9 definitions), few studies offered descriptions of the protocol followed or the process used to assign cause of death, and no study provided a thorough discussion of biases and limitations of their data. Additionally, some studies in the Poor category found smaller or larger proportions of maternal death attributable to abortion than what is suggested by the general literature or other studies in a similar geographic region. When such findings occurred, studies rated *Poor* were most likely to dismiss the results of other studies, or ignore the contradiction all together. One such discrepancy can be found in the paper by Mswia et al [40]. Despite the prospective nature of the study, and the explanation of protocol used to assign cause of death, significant variations in distribution of cause of death are found across study sites. Though the authors claim that the rural sites are similar in size and socio-economic make-up, no explanation is provided about factors that might be considered as driving the differences in distribution of cause of death across sites, nor is any discussion devoted to the discrepancy between the studies' finding of abortion related deaths (7.4% of maternal deaths) and other studies that have suggested a higher proportion (up to 20% of maternal deaths[1, 28]) in East Africa.

Six out of thirty-six studies received a rating of *Very Poor*. All studies in this category were facility-based studies, though the directionality of the study designs varied, none of the studies receiving a *Very Poor* rating used multiple sources of data to identify maternal deaths. None of these studies reported any definition of abortion, and few provided any description of the process or protocol followed in the assignment of cause of death. The discussion sections of these papers were found to be severely lacking, and most of the studies in the *Very Poor* category failed to discuss any limitations of the study or the data.

Discussion

A few notable trends emerge with respect to the quality of studies in this systematic review. First, more than half (54%) of all studies reviewed were categorized in the lowest two possible categories of quality ratings, and not one study achieved the highest possible quality rating. Such results highlight the need for a thorough examination of data sources, data collection techniques, and study reporting in the maternal mortality literature. Second, even among studies receiving a *Very Good* rating, where maternal mortality estimates were determined to be more valid, the risk of bias in the data reported was moderate to high. While some studies acknowledged the presence of selection bias or misclassification only one study addressed potential biases by using multiple techniques in attempt to validate results[39] and not one study out of thirty-six presented any quantitative assessment of the role of potential biases on their results. Recent developments in analytic tools that allow for the evaluation of sensitivity to multiple potential sources of systematic error and bias[41-43], could be extremely productive when applied to estimates of abortion related mortality. Third, the majority of studies in this systematic review failed to provide a clear definition of abortion, or abortion-related mortality. Without a standard definition, it becomes nearly impossible to compare results across studies or draw conclusions regarding trends of abortion related mortality globally, regionally, or locally. Some controversy surrounding the definition does indeed exist; while the current ICD-10 standard is to separate induced abortion from spontaneous abortion[10] when measuring incidence of abortion as well as abortion-related death, some have suggested that the risk of misclassification, in both directions, indicates that induced and spontaneous abortions should be measured as one category[24]. Regardless of which measure is ultimately chosen, it is imperative that the field settle on a clear and precise definition of abortion.

An additional trend emerges from the results of studies in this systematic review; on average, studies of higher quality reported estimates of abortion-related mortality that were higher than the estimates of abortion-related mortality reported by studies of lower quality. While meta analysis of the studies included in this review was not possible, this finding supports the widely stated position that current estimates of maternal mortality due to unsafe abortion, which are primarily estimated from resource poor settings where high quality data collection is most challenging,[1] are likely under-estimating the true burden of unsafe abortion-related mortality.

While many studies in the review had substantial limitations, this systematic evaluation allowed identification of key directions for improvement of future research. Improvements in the quality of data sources and data collection are the ultimate solution to better understanding global abortion-related mortality, and recent calls for investments from the global community in vital registration systems for all countries may go a long way to addressing such issues.[2, 12, 44] In the mean time, the field should encourage better reporting of study procedures and standardization of the definition of abortion and abortion-related mortality, and should support the use of multiple bias analysis techniques in the reporting of data, a method that could greatly aid the interpretation of results from studies seeking to quantify abortion related mortality.

Table 1: Evaluation Criteria for Study Rating

Evaluation Criteria	+ (Positive Rating)	+/- (Satisfactory Rating)	-(Negative Rating)
Study Design	Multiple sources of data were gathered/reviewed in order to identify as many maternal deaths as possible	More than one source of data was gathered/reviewed in the identification process for maternal deaths	Only one data source was gathered/reviewed in the identification process for maternal deaths
Diagnostic Procedures for COD Assignment	Diagnostic procedures followed standard international guidelines for COD assignment	A non-standard protocol was specified and followed	No protocol was specified
Definition of Abortion	One of the internationally accepted definitions of abortion was provided	N/A	No definition of abortion was provided
Study Reporting	All of the following conditions were met: 1) Thorough description of study design population, and facility characteristics was provided, 2) specific procedures for data collection, management, and analysis were reported, and 3) actual counts of maternal deaths and deaths by cause were reported	Two of the following conditions were met: 1) Thorough description of study design population, and facility characteristics was provided, 2) specific procedures for data collection, management, and analysis were reported, and 3) actual counts of maternal deaths and deaths by cause were reported	One or fewer of the following conditions were met: 1) Thorough description of study design population, and facility characteristics was provided, 2) specific procedures for data collection, management, and analysis were reported, and 3) actual counts of maternal deaths and deaths by cause were reported
Risk of Bias			
Negligible/ Very Low	Multiple sources of bias were identified and minimized and or accounted for in study design or analysis AND authors discussed in detail limitations of data with regard to interpretation.		
Low	Either multiple sources of bias were identified and minimized/accounted for in study design or analysis OR detailed discussion of limitations was provided.		
Moderate	Some bias was minimized through study design or analysis and some discussion of limitations was provided.		
High	Little to no bias was minimized through design or analysis, and little to no discussion of limitations was provided.		
Very High	|No bias was identified or minimized through design or analysis and no discussion of limitations of data was provided.		

Table 2: Rubric for evaluation of study quality

Quality Level	Study Design	Diagnostic Procedures for COD Assignment	Definition of Abortion	Study Reporting	Risk of Bias
Excellent	+	+	+	+	Negligible/ Very Low
Very Good	+	+	+	+	Low
Fair	+/-	+	+	+/-	Moderate
Poor	+/-	+/-	+	-	High
Very Poor	-	-	-	-	Very High

+ indicates a "Positive" rating
+/- indicates a "Satisfactory "rating
- indicates a "Negative" rating

Table 3: Summary of major study findings

Study (country)	Study Design, Period of data collection	Sources of mortality data	Description of study sample, number of maternal deaths	Number of Abortion related deaths/proportion of MDs due to abortion	Risk of Bias
Quality Rating: Very Good					
Zakariah, et al. 2009[45]. (Accra, Ghana)	RAMOS. One year (2002)	Medical records (admission and discharge books), death certificate books, death registers, mortuary logbooks and individual case notes	All maternal deaths occuring in Accra, Ghana during study period. **179** maternal deaths.	**37** abortion related deaths (**20.8%** of all maternal deaths)	**Low**. It is possible that some deaths that were not reported to any of the multiple data sources for mortality, were not recorded by the study.
Ramos, et al. 2007[46]. (Argentina)	Multi-center, population based, prospective study using RAMOS. One year (2002)	Hospital/clinical records, discharge records, death certificates, verbal autopsies	All maternal deaths occuring in 5 provinces with highest MMR in Argentina during the study period. **121** maternal deaths.	**33** abortion related deaths (**27.4%** of all maternal deaths)	**Moderate.** Despite the authors best efforts, because of the highly restrictive status of abortion in Argentina, it is likely that some under-reporting of abortion related deaths may be reflected in the data, and there is no discussion of potential biases or misclassification that might be involved in this analysis.
McCaw-Binns, et al. 2008[47]. (Jamaica)	Monthly active surveillance to identify and document the deaths of all women between 15 and 49 years of age, with evidence of pregnancy. Six years (1998-2003).	Admission registers for all hospital morgues and wards, discussions with health care providers, local district registrars, funeral homes, parish police headquarters, traditional birth attendants records	All maternal deaths occuring in Jamaica during study period. maternal deaths. **540** maternal deaths	**24** aboriton related deaths (**4.4%** of all maternal deaths)	**Moderate**. Despite the authors herculean data collection efforts, as they acknowledge,abortion related deaths are likely underreported and/or misclassified.
McCaw-Binns, et al. 2007[48]. (Jamaica)	Active surveillance of maternal deaths in public hospitals in Jamaica. Six years (1998-2003).	Institutional death and casualty registers and delivery books, case notes	All maternal deaths occuring in public hospitals in Jamaica during the study period. **232** maternal deaths.	**13** abortion related deaths (**5.6%** of all maternal deaths)	**Moderate.** Despite the authors confidence that nearly all (if not all) maternal deaths in public facilities were indeed captured, because of the sensitive nature of abortion, it is likely that aboriton related deaths are under-reported and/or misclassified.
Chowdhury, et al. 2007[49]. (Matlab, Bangladesh)	Cohort study. Thirty years (1976-2005)	Monthly household visit semi-structured questionnaire with relatives of all women who died when aged 15–49 years, verbal autopsy, routine demographic surveillance.	All maternal deaths identified in two neighboring areas in Matlab during the 30 year cohort study. **769** maternal deaths.	**143** abortion related deaths (**18.6%** of all maternal deaths)	**Low-Moderate.** Despite the exceptional data collection processes and the extensive interviewer training program, even under such ideal circumstances the authors note that some misclassification may have occurred.

Study (country)	Study Design, Period of data collection	Sources of mortality data	Description of study sample, number of maternal deaths	Number of Abortion related deaths/proportion of MDs due to abortion	Risk of Bias
Sloan, et al. 2001[39]. (Mexico)	Re-analysis of verbal autopsy study conducted on all reported maternal deaths in three Mexican states. One year (1995).	Verbal autopsy, all known sources of death records, death certificates, additional follow-up verbal autopsy.	All maternal deaths reported over the study period. 145 maternal deaths.	Various analytic methods used, revealed a range of **1.4-5.5%** of all maternal deaths	**Moderate.** Despite the authors best attempts and their acknowledgement of the limitations of their data, there is still the distinct possibility that these data have been biased by self-report and the lack of standardization in attribution of COD.
Chowdhury, et al. 2009[50]. (Matlab, Bangladesh)	Retrospective review of multiple sources of secondary data. Thirty years broken into three, 10-year intervals (1976-1985, 1986-1995, 1996-2005) for two areas of Matlab, Bangladesh where services are provided by ICDDRB and Government Administration respectively.	Health and Demographic Surveillance System data, pregnancy- monitoring cards, facility records for pregnancy and delivery care at the Matlab Hospital and sub- centres, verbal autopsies, the Matlab Health and Socioeconomic Survey (1996), and periodical socio- economic censuses (1982, 1996, and 2005). Verbal autopsies conducted during 1976-2005 under the HDSS, special maternal death reviews to validate maternal deaths.	All maternal deaths identified from all sources of data during study period. *1976-1985, ICDDRB*: **413** MDs. *1976-1985, Gov:* **479** MDs. *1986-1995, ICDDRB:* **342** MDs. *1986-1995, Gov*: **386** MDs. *1996-2005, ICDDRB:* **180** MDs. *1996-2005, Gov.:* **279** MDs.	1976-1985, ICDDRB: **97** Abortion related deaths (ARDs) (**23.5%** of all MDs). 1976-1985, Gov: **81** ARDs (**17%** of all MDs). 1986-1995, ICDDRB: **59** ARDs (**17.3%** of all MDs). 1986-1995, Gov: 85 ARDs (**22%** of all MDs). 1996-2005, ICDDRB: **20** ARDs (**11.1%** of all MDs). 1996-2005, Gov.: **42** ARDs (**15%** of all MDs).	**Low-Moderate.** The authors offer an excellent discussion of the role of Menstrual Regulation in the decline of abortion related mortality, including increased access to contraceptives, increasing safety of MR, and increasing education of women. Nevertheless, there may still be some misclassification or underreporting of abortion related deaths, especially earlier on in the data.
Zakariah, et al. 2006[51]. (Accra, Ghana)	Retrospective review of deaths in 4 main hospitals. One year (2000).	Three sources of hospital records were used: admission and discharge (A&D) books, mortuary pathology records, and hospital death certificate books. All death registers from 12 of the 13 registries in the Greater Accra region, retrospective reproductive age maternal mortality survey was done in the four major hospitals.	All maternal deaths identified from all sources of data during the study period. **148** maternal deaths.	**42** abortion related deaths (**17.6%** of all maternal deaths).	**Moderate.** Despite the exceptional data collection processes and the extensive efforts to capture ALL deaths in facilities, the authors note that 86% of deaths in Accra occur in facilities. The results could suffer from some selection bias with relationship to the general population of Accra, additionally the facility data themselves may suffer from misclassification and/or underreporting of such deaths.

Study (country)	Study Design, Period of data collection	Sources of mortality data	Description of study sample, number of maternal deaths	Number of Abortion related deaths/proportion of MDs due to abortion	Risk of Bias
Bartlett, et al. 2005[52]. (Afghanistan)	Two phase, retrospective, nationally representative cohort study. Three years (1999-2002).	Death identification survey, verbal autopsy.	All maternal deaths identified for which verbal autopsies could be conducted due to safety concerns. **133** maternal deaths.	**1** abortion related death (**1%** of all maternal deaths)	**High.** Despite the nationally representative nature of these data, and despite the rigor used in interviewing, and classification of death, due to the insecurity of the region interviewers were not able to conduct VA on all identified MDs, and could not report differences between populations. In addition, the restrictive nature of abortion in Afghanistan likely leads to underreporting and misclassification of abortion related death in these data.
Jafarey, et al. 2009[53]. (Pakistan)	Ambi-directional cohort study. Three years (2005-2007)	Monthly reports of Lady Health Workers; health management information system (HMIS), records of public-sector hospitals, records of private hospitals, graveyards, and union councils, Special survey on community factors, and Verbal Autopsy	All maternal deaths identified from all sources of data during study period. **128** maternal deaths.	**1** abortion related death (**1%** of all maternal deaths)	**High**. Despite the authors very best efforts, abortion related deaths are significantly underrepresented and, likely because of stigma associated with abortion and restrictive legal status of abortion, is likely under-reported and/or misclassified in these data.
Quality Rating: Fair					
Campbell, et al. 2005[54]. (Egypt)	Nationally representative cohort study. Two, one year studies (1992-1993, and 2000).	Verbal autopsy	All maternal deaths identified through verbal autopsy during study periods. 1992-1993: **772** MDs. 2000: **585** MDs.	1992-1993: **13** abortion related deaths (**3%** of all maternal deaths). 2000: **6** abortion related deaths (**1%** of all maternal deaths).	**High.** Despite the nationally representative nature of these data, no attempt to validate results of verbal autopsy is made, and no discussion is devoted or effort is made to correct potential misclassification or other validation issues. Due to the restrictive legal climate for abortion in Egypt, the reported figures are likely underestimates.
Geelhoed, et al. 2003[55]. (Ghana).	Active surveillance of maternal deaths in a district Hospital. Thirteen years (1998-2003).	Medical records (deaths of females of reproductive age in labor ward, maternity ward, female ward, and emergency room)	All maternal deaths occuring over the study period (13 years) in Bekerum district Hospital. **229** maternal deaths.	**43** abortion related deaths **(18.8%** of all maternal deaths)	**Moderate**. despite the authors best efforts, some bias may still exist in the reporting of abortion-related deaths

Study (country)	Study Design, Period of data collection	Sources of mortality data	Description of study sample, number of maternal deaths	Number of Abortion related deaths/proportion of MDs due to abortion	Risk of Bias
Verma, et al. 2001[56]. (Ludhiana, India)	Retrospective review of medical records. Ten years (1985-1995).	Hospital records of all obstetrics cases, emergency department, ICU, and general hospital death records for women of reproductive age.	All maternal deaths identified from the medical records during the study period. **116** maternal deaths.	**44** abortion related deaths (**41.9%** of all maternal deaths.)	**Moderate.** Procedures for this study are standardized well, and a reasonable attempt is made to capture all maternal deaths. However, due to the fact that these data are hospital data, the authors note that there may be an over-representation of abortion related deaths because only the most serious cases end up in facilities. Therefore the data may not be representative of the larger population, but may, infact provide a good estimate of the proportion of facility-based maternal deaths that are abortion related.
Bell, et al. 2008[57]. (Burkina Faso)	Census. Five years (2001-2006)	Census data, verbal autopsy	All pregnancy related deaths identified through census and verbal autopsy. **385** pregnancy related deaths	abortion related deaths account for **6.5%** of all pregnancy related deaths.	**Moderate-High**. Census data have been shown to have insurmountable biases related to the accurate capture of mortality (recall bias) and especially maternal mortality. Additionally, despite the authors best efforts to identify some of the limitations of this study, biases surrounding the reporting of abortion and abortion related deaths, nevertheless exist.
Oyieke, et al. 2006[58]. (Nairobi, Kenya)	Retrospective review of medical records. Five years (1995-1999).	Case notes of all maternal deaths during pregnancy, delivery and the puerperium, records in the statistics section of the hospital records department	All maternal deaths identified during the study period. **203** maternal deaths.	**53** abortion related deaths (**25.6%** of all maternal deaths)	**Moderate-High.** The high incidence of abortion related deaths may indicate the role of selection bias due to the referral nature of the hospital. Additionally, there is 20% loss to follow up in the record review, and no description is offered of characteristics of those lost to follow-up or comparison with those in the study, the reader therefore cannot assess whether biases are present.
Mogobe, et al. 2007[59]. (Botswana)	Retrospective review of National Maternal Mortality Audit Commit- tee analyses. Two years (2004-2005).	Confidential Maternal Death Notification Form	All maternal deaths identified in facilities in Botswana during the study period. **116** maternal deaths.	**4** abortion related deaths (**3%** of all maternal deaths)	**High**. Facility based data are unlikely to be representative of the population of Botswana, which appears to be the target population for the study. In additoin, abortion comprises 3% of maternal deaths identified, a dramatic reduction from other figures for the region, indicating the presence of underreporting and/or misclassification with respect to abortion related deaths

Study (country)	Study Design, Period of data collection	Sources of mortality data	Description of study sample, number of maternal deaths	Number of Abortion related deaths/proportion of MDs due to abortion	Risk of Bias
Quality Rating: Poor					
Aboyeji, et al. 2007[60]. (Ilorin, Nigeria)	Retrospective review of medical records. Six years (1997-2002).	Hospital records of maternal deaths (unspecified sources)	All maternal deaths identified from medical records during the study period. **108** maternal deaths.	**16** abortion related deaths (**14.8%** of all maternal deaths).	**High**. Diagnostic criteria for assignment of cause of death are not provided, no attempt to account for deaths that might have been missed because of retrospective nature of data collection, no discussion of or attempt to account for the highly restrictive legal status of abortion or potential misclassification/under-reporting this might produce. Estimates likely biased.
Fabamwo, et al. 2009[61]. (Ikeja, Nigeria)	Two designs reported: Prospective cohort and Case-Control. Three years (2000-2003)	All admitted cases of induced abortion confirmed by the patients or accompanying relations and carried out in other facilities and with specific complications.	All maternal deaths identified from all admited cases of induced abortion during the study period. **158** maternal deaths.	**39** abortion related deaths (**24.7%** of all maternal deaths).	**Moderate.** Because this study sought to capture all abortion related complications, bias relating to deaths from induced abortion is minimized. However, due to the restrictive nature of abortion in Nigeria, some underreporting and/or misclassification could still be present in the data. Additionally, because this is an urban, tertiary-care hospital, these data may not be representative of the general population which the hosptial serves (because the most serious cases are referred to this hospital, data may even reflect overestimates).
Panchabhai, et al. 2009[62]. (India)	Retrospective review of medical records and autopsy record. Eight years (1998-2006)	Hospital medical records (unspecified sources), pathology department autopsy reports.	All cases of maternal deaths autopsied by the pathology department during the study period. **277** maternal deaths.	17 abortion related deaths (**6.1%** of all maternal deaths)	**Moderate-High**. The dataset includes only those cases for which autopsy was performed (just over half of all maternal deaths observed during the study period), this could significantly bias the data with regard to distribution of cause of death, and since no explanation is provided of the reasons for non-autopsy, and no effort to compare those maternal deaths that were excluded with those that were included, it is impossible to evaluate whether the data are biased.

Study (country)	Study Design, Period of data collection	Sources of mortality data	Description of study sample, number of maternal deaths	Number of Abortion related deaths/proportion of MDs due to abortion	Risk of Bias
Granja, et al. 2001[63]. (Mozambique)	Retrospective review of medical records. Five years (1989-1993).	Medical records, antenatal records if available, and autopsy records	All maternal deaths identified during the study period. **239** maternal deaths.	**18** abortion related deaths (**7.5%** of all maternal deaths)	**High**. Some discrepancies were found with respect to the distribution of causes between this study and others from Mozambique, no explanation is offered for the differences, nor is any attempt made to understand potential misclassification or underreporting for different causes of death.
Puri, et al. 2011 [64].(Delhi, India)	Retrospective review of medical records. Four years (2003-2006)	Hospital medical records (unspecified sources)	All maternal deaths recorded at Hindu Rao Hospital during the study period. **130** maternal deaths.	**6** abortion related deaths **(4.6%** of all maternal deaths).	**High.** The data collection process is poorly described, there is no understanding about what the target population is indended to be, and no discussion about potential biases present in the review, collection, or assessment of the medical records. The low proportion of abortion related deaths, given the setting, likely indicates the presence of bias.
Mswia, et al. 2003[40]. (Tanzania)	Prospective sentinal surveillance of maternal deaths. Eight and one half years (1992-1999).	Sentinal system mortality records, verbal autopsy	All maternal deaths identified in three discricts of Tanzania during the study period. **441** maternal deaths.	**8** abortion related deaths (**7.4%** of all maternal deaths)	**High.** Classification of maternal deaths is based on self report, there are major differences in COD that vary by site, and no explanation is offered, no discussion of the major differences between 'induced' and 'spontaneous/unspecified' across sites, no discussion of potential biases this might suggest.
Daramola, et al. 2005[65]. (Lagos, Nigeria)	Retrospective review of medical records. Ten years (1989-1998).	Medical records including autopsy protocols, case notes	All maternal deaths identified during the study period on which sufficient clinical data and autopsy certification were present. **230** maternal deaths.	**24** abortion related deaths (**10.4%** of all maternal deaths)	**High.** There is no discussion of the differences between those who were not included in the study and those who were due to lack of clinical data or lack of autopsy, with regards to abortion related deaths this could result in serious under-reporitng, in addition to overall issues of potential underreporting and misclassification of abortion related deaths which is not discussed.

Study (country)	Study Design, Period of data collection	Sources of mortality data	Description of study sample, number of maternal deaths	Number of Abortion related deaths/proportion of MDs due to abortion	Risk of Bias
Oi, et al. 2007[66]. (Lagos, Nigeria)	Retrospective review of abortion related complications and maternal deaths. Four years (2000-2003)	Hospital records of maternal deaths(unspecified sources)	All maternal deaths identified during the study period, all abortion related complications identified during the study period. **194** maternal deaths.	**39** abortion related deaths **(20.7%** of all maternal deaths). *Study reports 24.7% but this is inaccurate.*	High. This study was focused on quantifying abortion-related complications, and thus their search strategy first selected abortion related complications and was able to capture all deaths from abortion deaths, minimizing bias. However, documentation procedures are unclear, little known about population, and despite the advantages of the data collection process some bias (selection, underreporting, misclassification) may still exist.
Jain, et al. 2004[67]. (India)	Retrospective review of medical records. Twelve years (1988-2002).	Hospital records of all obstetrics cases, emergency department, ICU, and general hospital death records for women of reproductive age, specific review or emergency admissions due to abortion related complications.	All maternal deaths occuring in the hospital during the study period. **545** maternal deaths.	**93** abortion related deaths (**17.1%** of all maternal deaths).	**Moderate.** Because the study was conducted in a tertiary hospital, these deaths cannot be assumed to be representative of the general population, and can only be generalized to those with the worst complications.
Abdel-Hady, et al. 2007[68]. (Dakahlia, Egypt)	Prospective cohort study. Two year (2004-2005)	Confidential enquiry, review of the patient's notes from public health facilities, Mansoura University Teaching Hospital, reports from doctors and nurses at private health facilities	All maternal deaths identified from all sources of data during study period. **179** maternal deaths.	**5** abortion related deaths (**2.8%** of all maternal deaths)	**Moderate-High**. concerted effort is made to capture all maternal deaths in the study area by triangulating all available data sources. In Egypt, where most women deliver in hospitals, this may be a fairly complete count. However, the authors offer no discussion of how COD was attributed (to what standard), no discussion of abortion/legal context or potential misclassification, very little is known about the population, and very little is known about the research process, thus it difficult to judge how good the data might be without more contextual information.

Study (country)	Study Design, Period of data collection	Sources of mortality data	Description of study sample, number of maternal deaths	Number of Abortion related deaths/proportion of MDs due to abortion	Risk of Bias
Bergsjo, et al. 2008[69]. (Moshi, Tanzania)	Retrospective review of medical records. Five years (2000-2004).	Hospital medical records (unspecified sources), Case Notes, Maternal Death Registration Form.	All maternal deaths registered at Kilimanjaro Christian Medical Centre during study period. **119** maternal deaths.	**2** abortion related deaths **(1.7%** of all maternal deaths)	Moderate. This study made a concerted effort to go back through all records that may not have been properly recorded and attempt to address some of the potential bias/missing data, however, the authors acknowledge that bias from underreporting and potential misclassification may exist. Additionally, no description is given vis a vis the definition of abortion, or other COD.
Lema, et al. 2005. (Blantyre, Malawi)	Retrospective review of medical records. Two years (1999-2000).	Hopsital records from gynecological, labour, antenatal and postnatal wards, maternity, operating theatre and intensive care unit.	All maternal deaths identified during the study period. **204** maternal deaths.	**48** abortion related deaths (**23.5%** of all maternal deaths)	**High.** No definitions are provided, system used for COD attribution not described, no discussion of what data might have been missed due to the retrospective nature of data collection and/or underreporting and misclassification. Because this is a eferral hospital it is likely to see higher proportion of serious cases and no discussion is devoted to representativeness of data to population.
Almerie, et al. 2010[70]. (Damascus, Syria)	Retrospective review of medical records. Twenty years (1989-2008).	Hospital medical records (unspecified sources)	All maternal deaths identified during the study period. **189** maternal deaths.	**4** abortion related deaths (**2.1%** of all maternal deaths)	**High**. No definition of abortion is provided, nor are criterea used to define other causes of death, no discussion of the legal status of abortion is provided, nor any potential limitations of measuring COD, no characteristics of the population, the area, or the facility are provided at all, so the quality of the data are very difficult to assess.
Supratiko, et al. 2002[71]. (Indonesia)	District-based audit of maternal mortality.	District hospital records, Health center records, midwives reports, post-mortem interviews	All maternal deaths identified from all sources of data during study period. **130** maternal deaths.	**2** aboriton related deaths (**3.6%** of all maternal deaths)	**High.** Data-collection strategy is not adequately described. No definition of Maternal Death is provided, the assignment of COD is not described, nor is the algorithm or instrument used described at all.

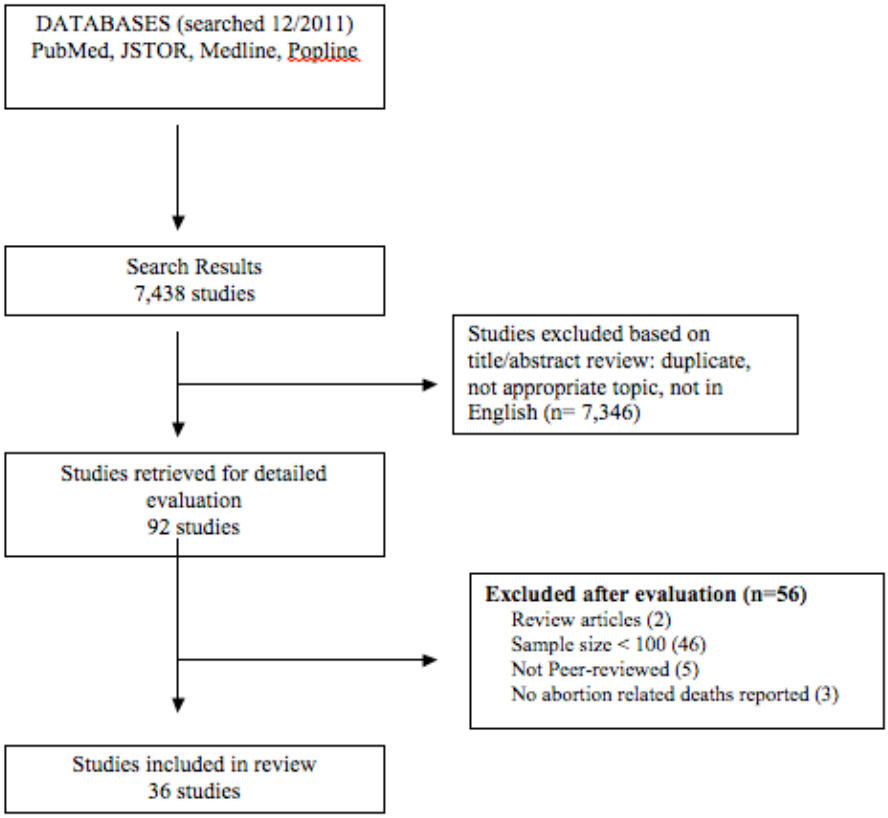
Study (country)	Study Design, Period of data collection	Sources of mortality data	Description of study sample, number of maternal deaths	Number of Abortion related deaths/proportion of MDs due to abortion	Risk of Bias
Quality Rating: Very Poor					
Chhabra, et al. 2004[72]. (Maharashtra, India)	Retrospective review of medical records for all maternal deaths due to hemmorhage. Twenty years (1982-2002).	Case records of all maternal deaths, specifically those due to haemorrhage at Mahatma Gandhi Institute of Medical Sciences.	All maternal deaths identified during the study period. **201** maternal deaths.	**4** abortion related deaths (**2.0%** of all maternal deaths)	**High.** No definition of maternal death is provided, no definition of abortion is provided. There is no discussion of procedure around assignment of COD or how misclassification might possibly come into play, while there is some analysis of trends over time, there is no attempt to validate the statistical significance of those trends, nor discuss biases or limitations to the data.
Iyengar, et al. 2009[73]. (Rajasthan, India)	Cross-sectional Verbal Autopsy and Maternal mortality audit for deaths in past year. One year (2002-2003)	General information form, pregnancy-related death, death due to illness, and injury-related death, and care-seeking form.	All maternal deaths identified in 14 blocks in Rajasthan, India during the study period. **156** maternal deaths.	**2** abortion related deaths **(1.3%** of all maternal deaths)	**High**. This study attempted to use a verbal autopsy audit methodology, but the methodology is poorly described, a clear definition of maternal death is not provided, The authors do not provide a definition of abortion, or how they attempted to fully capture abortion related deaths
Ujah, et al. 2005[74]. (Plateau State, Nigeria)	Prospective cohort study. Seventeen years (1985-2001)	Case files of all women dying in pregnancy and childbirth in the maternity unit of the hospital, interviews with relatives	All maternal deaths identified at the Jos University Teaching Hospital during the study period. **267** maternal deaths.	**30** abortion related deaths (**9.4%** of all maternal deaths).	**Moderate.** While this study collected data prospectively for 17 years, the authors provide no definition of maternal death, no definiton of abortion, and offer no discussion of the potential for missing cases, selection bias with respect to the general population, or any issues of underreporting and/or misclassification which are likely present in the data.
Okonota, et al. 2002[75]. (Afikpo, Nigeria)	Retrospective review of medical records. Ten years (1990-1999).	Delivery, abortion, 'born before arrival', and maternal death registries at Mater Misericordiae Hospital	All maternal deaths identified during the study period. **104** maternal deaths.	**4** abortion related deaths 4**.8%** of all maternal deaths)	**High**. The authors provide no discussion of procedures or metrics used to identify maternal deaths or assign cause of deaths, and no discussion of abortion status of possible biases despite the marked departure from 10-25% of MM that are generally understood to be abortion related deaths in Nigeria.

Study (country)	Study Design, Period of data collection	Sources of mortality data	Description of study sample, number of maternal deaths	Number of Abortion related deaths/proportion of MDs due to abortion	Risk of Bias
Mariaga, et al. 2009[76]. (Bauchi, Nigeria)	Prospective cohort study. Seven years (2001-2007)	Hospital medical records (unspecified sources), case notes	All maternal deaths identified at State Specialist Hospital Bauchi, during the study period. **767** maternal deaths.	**48** abortion related deaths (**6.3%** of all maternal deaths)	**High.** Despite the large sample size, no description of the data collection procedure or the cause of death assignment is provided, the distribution of COD differs fairly significantly from the distribution that other studies have reported for Nigeria.
Kullima, et al 2009 (Northern Nigeria)	Retrospective review of medical records. Five years (2003-2007).	Hospital case notes.	All maternal deaths discerned from case notes of pregnant women admitted into the medical center during the study period. **112** maternal deaths.	**7** abortion related deaths (**6.2%** of all maternal deaths).	**High.** This study has few merits. while it seems to suggest that it is a complete report of all maternal deaths that occurred in the facility over 5 years, it does nothing to substantiate those claims; no definition of maternal death is provided, no diagnostic procedures are provided with regard to the assignment of COD, no discussion of biases is given, no attempt to identify misclassification.

Table 4: Proportion of abortion related deaths reported by study quality

Rating (n)	Median	Range
Excellent	--	--
Very Good (10)	16	1-27.4
Fair (6)	6.5	1-41.9
Poor (14)	7.45	1.7-24.7
Very Poor (6)	2	1.3-9.4

Figure 1
Systematic Review Search Strategy



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Chapter 2

Systematic Error in Estimating Unsafe Abortion Related Maternal Mortality: A Framework and Multiple Bias Analysis

Background:

Measurement of All-Cause Maternal Mortality

In recent years, notable developments have advanced the techniques for estimating all-cause maternal mortality on a national level. First, methodological progress has allowed for the correction of some common biases in population-level maternal mortality surveys. Secondly, a careful review of national vital registration data by the Global Burden of Disease study has resulted in the correct classification of female deaths which were previously unclassified or misclassified, as maternal deaths[1]. Third, statistical advances have led to new modeling techniques for maternal mortality based on new and existing data[2]. Capitalizing on these advances, in 2010 two independent studies using competing modeling algorithms, estimated that approximately 350,000 maternal deaths occurred globally in 2008 (the most recent year for which data are available) with confidence intervals from 295,000 to 503,000 (Murray and WHO). Each study produced national estimates of all-cause maternal mortality for 181 countries with varying levels of precision. A recent analysis[3] of the two studies that published conflicting estimates of global levels of maternal mortality in 2010[2,4] comes to the conclusion that, while some advances have been made, and while numerous methods exist for the measurement of all-cause maternal mortality, none of the existing methods can produce unbiased estimates.

There are myriad approaches to measuring maternal mortality, specifically: National vital registration systems, census data, population-based household surveys, Health Information and Management Systems (HIMS) data, Reproductive age mortality surveys (RAMOS), and verbal autopsy studies. Each approach is limited by several sources of bias. Hill[5] and colleagues have examined national vital registration systems – considered by many to be the gold-standard for mortality measurements—have shown how the countries implementing these systems do not detect 30-50% of all maternal deaths. Compounding the biases in estimating a global total for maternal mortality, 75% of births take place in countries without a national vital registration system[5-11].

Nationally-representative, population-based household surveys use the sisterhood method (an indirect method which involves asking each interviewee how many sisters he/she has, and how many of the sisters have died during the perinatal period) to estimate national maternal mortality over a defined period of time. These household surveys are capital and labor intensive, are subject to interviewer and respondent bias, and problems with recall, and thus have been shown to underestimate the true maternal mortality ratio[12].

Health Information and Management Systems(HIMS), which collect vital data from health facilities, are the primary source of mortality data in countries without vital registration systems. HIMS are known to miss, or misclassify maternal deaths, in part because most deaths in countries without comprehensive vital registration systems occur outside of health facilities[13]. For the deaths occurring in the health facility, data are of poor quality due to insufficiently detailed case-notes[14,15], inconsistent facility-wide reporting[14], and loss of records[15].

Verbal autopsy is a World Health Organization (WHO) validated tool used to attribute cause of death where comprehensive vital registration systems do not exist. An interviewer contacts a surviving family member to collect detailed, quantitative data on the circumstances of death. The verbal autopsy method is complicated to implement,

requires intensive training, has varying levels of sensitivity and specificity for different causes of death, and is subject to both interviewer and reporting biases[16].

Reproductive Age Mortality Surveys (RAMOS) are also thought to underestimate maternal deaths[17]. The RAMOS method uses a combination of vital registration data and verbal autopsy methods to estimate maternal deaths are dependent upon the completeness of vital reporting, and are subject to the same biases that affect verbal autopsies[17].

Finally, census data, due to long periods of recall and questionable phrasing have been shown to produce inaccurate reports of maternal mortality, and have been widely discarded as a valid source of data for national estimates of maternal mortality[18].

Given the wide-spread underreporting of maternal mortality by families and interviewers, as well as other biases known to be present in current estimating techniques for maternal deaths, adjustment factors have been used to compensate for under-estimations of maternal mortality in the modeling of national and global estimates[2,4,5]. Given that the formulae for deriving the adjustment factors employ national birth and death rates, such adjustments can only be applied to mortality estimates derived from nationally representative data[5].

Recent calls for improved data collection on global maternal mortality point toward the importance of strengthening vital registration systems[14,19], with specific focus on the five primary causes of maternal death globally: hemorrhage, hypertensive disorders, sepsis, abortion, and obstructed labor[13,14,19]. In recent years, it has been demonstrated that the most precipitous reductions in maternal mortality occur in settings where interventions target the most prevalent individual obstetric causes of death[20]. Absent accurate measure of cause-specific maternal deaths, maternal mortality interventions may focus on programs for which the total impact will be limited[21-23].

Measurement of Abortion-Related Mortality

While each obstetric causes of death presents its own, unique measurement challenges, abortion-related death is arguably the most challenging to measure[24-26]. Relative to the challenges in the estimation of the burden of other primary causes of maternal mortality, unsafe abortion-related maternal mortality faces especially challenging barriers. In countries where abortion is illegal or highly restricted, such barriers include social stigma, religious norms, and legal repercussions. Virtually all abortion related deaths are preventable. Abortion, when performed under safe and sterile conditions, is one of the safest medical procedures currently available, but, because of the barriers that women face in accessing safe abortions services, mortality and morbidity from unsafe abortion is all too common in the developing world. Because abortion related death is so challenging to measure, it is nearly impossible to understanding the full extent of the burden of abortion related mortality. Without accurate measurement we cannot effectively target programs to reduce the dangerous consequences of unsafe abortion.

Of the measurement approaches previously discussed for estimation of overall maternal mortality, facility-based HIMS data and verbal autopsy are at present the only available measurement tools to assess cause-specific maternal mortality[27]. Because of the social and legal barriers that exist, it is likely that data collected through facility-based surveys about unsafe abortion-related mortality does not accurately capture the magnitude of abortion-related mortality in the facility's catchment area[28]. For example, if women who experience unsafe abortions were systematically less likely to seek medical

services if they experience complications than women who experience complications from other maternal causes, the proportion of maternal mortality related to unsafe abortion in a facility's catchment area will be underestimated. Potentially creating a second bias, in the direction of over-estimation, studies of cause-specific maternal mortality that are conducted in referral facilities will capture women with the most severe maternal complications. If women who have unsafe abortions systematically experience more severe complications prior to death than women who experience other maternal causes of death, abortion-related mortality estimates from referral facilities would exhibit a second bias in the opposite direction[29]. While it is likely impossible to assess the individual effect of each biases on the estimation of the contribution of unsafe abortion to maternal mortality, methods such as multiple bias analysis[30], do exist which might provide some insight into the net effect of the many biases present.

Challenges with measuring abortion related mortality extend to verbal autopsy designs as well. While verbal autopsy may provide some advantages over facility-based estimates in estimating the community-level underlying distribution of cause-specific maternal mortality, concerns over selection bias persist: Due to wide-spread social and religious stigma, along with fear of legal ramifications, family members may be less likely to participate in verbal autopsy studies if the maternal death in question was abortion-related as compared to deaths from other maternal causes[27,31]. Additionally, in comparison to other obstetric complications, women are less likely to admit to family members that they are experiencing abortion-related complications[32-34] which can lead abortion-related deaths to be systematically misclassified as non-abortion-related maternal deaths, or even as non-maternal deaths[35].

Some biases are common to both facility-based and verbal-autopsy studies. Because women who experience complications from unsafe abortion often experience symptoms like heavy bleeding and infection, the literature suggests that clinicians who assign cause of death in facility-based studies and with verbal-autopsy forms can unintentionally misclassify unsafe-abortion related deaths as deaths from hemorrhage or sepsis[11,36,37]. Abortion-related deaths are more likely than the other maternal causes to be classified as "unknown" [26,37]. Additionally, in environments where physicians can face legal consequences if they provide medical care to patients who have induced abortion, intentional misclassification of abortion-related complications and deaths is common[3733]. If abortion related deaths are more likely to be misclassified as non-abortion related deaths, the misclassification will produce an underestimate of abortion-related deaths as a proportion of all maternal deaths.

Epidemiologic Approaches to Systematic Error

Studies that measure abortion-related mortality ultimately seek to present valid, precise, and generalizable estimates of the underlying 'burden of disease'. To achieve these goals, attention must be given to the potential for both random and systematic error present in the data. Epidemiologists have focused a great deal of attention on the development of accessible and interpretable methods for reporting random error within non-randomized studies[38,39], and while a substantial debate exists in the epidemiologic literature about the most appropriate method of assessing and describing random error[38,40-42], today the frequentist confidence interval and the p-value are most commonly reported[40]. Much less attention has been devoted to the treatment of systematic error in the

epidemiologic literature. Due to the necessity (ethical or practical) of non-randomized study designs, and imperfect measurement tools, some systematic error is present in most epidemiologic studies. Techniques for the quantitative assessment of systematic error have existed for decades[43], and range from simple sensitivity analyses[44] to complex Bayesian uncertainty analysis approaches[30]. Yet, it is only recently that calls have emerged in the epidemiologic literature to measure and report systematic error[30,45-48].

Some methodologically focused journals do make an attempt to publish sensitivity analyses of various kinds, however, most typically in the epidemiologic literature, assessment of systematic error is considered qualitatively in the discussion and limitations sections of a journal article. Evidence suggests that this qualitative approach will most often result in an underestimation of the role of systematic error[22], and that researchers themselves are prone to confirmation bias in their assessment of their own findings[49]. The broad lack of quantitative assessment of bias in published epidemiologic studies is tantamount to an assumption that no bias exists[30,44]. Given the availability of quantitative tools to assess systematic error in studies, surely it is preferable to acknowledge the limitations of our data and present more honest estimates, than fail to recognize potential biases and present data we know to be flawed.

While quantitative descriptions of random error in studies of abortion-related mortality could be improved, the tools are widely available, and adopting the use of confidence intervals for point estimates would be consistent with a wide body of epidemiologic literature on maternal mortality[1,3,45,46,50]. Analysis of the multiple sources of systematic error in studies of abortion-related mortality would require a paradigmatic shift towards the recognition that, despite myriad challenges in data collection, the validity of study results deserves the same rigorously quantitative treatment as the precision of those results.

This paper will present a multiple-bias analysis approach to quantify the effect of systematic error on abortion-related maternal mortality estimates, outline a simple framework for investigators interested in replicating a multiple-bias analysis in their own data, and suggest approaches to report such analyses in the literature.

Methods

Data Sources

We selected three studies at random to perform multiple bias analysis among the n studies which measured abortion-related maternal mortality in chapter 1. The studies will be referred to as *Study A, Study B, and Study C*.

Study A, by Jafarey, *et al*[47], was a study of maternal deaths between 2005-2007 in two subdivisions (Sukkur and Malir) of the Sindh district in South Eastern Pakistan, where abortion is legal only to save a woman's life. The joint aggregate population of the two subdivisions was approximately three million people. Primary healthcare workers (Lady Health Workers) identified maternal deaths (defined as the ICD-10 definition "the death of a woman while pregnant or within 42 days of termination of pregnancy irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes" [48] in communities using a modified version of the WHO verbal autopsy form via household survey. Data on maternal deaths were also collected from Health Management

Information System (HMIS), public and private sector hospital records, graveyards, and union councils. A three-member physician panel reviewed the verbal autopsy forms to assign cause of death, also according to ICD-10[48] definitions. The study found 128 maternal deaths, one of which was reported as a death from abortion-related causes. The authors acknowledge that the low proportion of abortion-related deaths was unlikely to be accurate, and was likely due to under-reporting. Despite the evident biases in the ascertainment of abortion-related mortality, the investigators' thorough data collection processes, validated survey instruments, and clear reporting earned the study a rating of "Very Good" in the prior systematic review.

Study B, a hospital based study by Mariaga and Saleh[51], prospectively measured maternal mortality in a state referral hospital in Bauchi State, in Northeastern Nigeria between January 2001 and December 2007. The total stated population of Bauchi State at the beginning of the study (2006 data) was 4.6 million people. One of the authors developed a data collection tool to identify maternal deaths from hospital case notes, and that author extracted all data for maternal deaths over the study period; the authors did not state from which wards or areas of the hospital the case notes were obtained. Maternal Death was defined by the ICD-10 definition[4845], the cause of death was registered on the data collection form, but the manner of ascertainment of the cause of death was not provided. The study identified 767 maternal deaths and 48 abortion related deaths. No discussion was provided of the potential effect of restrictive abortion laws on the identification of abortion-related deaths, nor was any discussion of the generalizablility of the estimates to the target population, which the reader assumed to be the entire population of Bauchi State. The poor descriptions of methods, non-validated measurement tools, and insufficient reporting of study data earned the study a rating of "very poor" in the systematic review.

Study C, was a facility-based study of maternal deaths from the maternity ward at the main referral hospital in Kenya (Kenyatta National Hospital) by Oyieke, *et al*[52]. While the authors never clearly stated the period of study, because annual estimates are provided for the years 1995-1999, it was assumed that those were the years under study. Data were collected from case notes from the maternity ward of the hospital, and extraction of data files from the study period was reported as 80% of the all maternal deaths identified in case notes. Maternal death was defined by the ICD-10 definition, but no description of the methodology for ascertaining cause of death was provided. The study identified 253 maternal deaths, of which 52 were abortion related. Some discussion was provided of the potential for missing data but no discussion was devoted to the additional challenges of ascertaining abortion-related deaths given the restrictive environment for abortion in Kenya. Brief discussion was devoted to potential problems of generalizability from a facility-based study to the entire country. Given the poor description of study design and the lack of clarity on measurement instruments, the study received a rating of "poor" in the systematic review.

Bias Framework

Figure 1 represents a bias framework for any study of abortion-related maternal deaths. We posit that these sources of bias are present in both verbal autopsy studies and facility-based studies. If, relative to women who do not experience abortion-related death, women who experience abortion-related deaths are more or less likely to arrive at health facilities and/or are more or less likely to be captured as maternal deaths through verbal autopsy, bias will arise (eg, the proportion of maternal deaths due to abortion measured in a study will differ from the proportion of maternal deaths due to abortion in the target population); this bias can be identified as selection bias. If, relative to women who do not experience abortion-related death, women who abortion-related deaths are more (or less) likely to be correctly classified as abortion-related deaths than other types of maternal deaths, bias will arise (eg, the sensitivity and specificity of abortion related-classification will differ from the sensitivity and specificity for deaths from other maternal causes, and the proportion of maternal deaths due to abortion in the study will differ from the proportion in the enrolled population), this bias can be identified as information bias, or misclassification.

Multiple Bias Analysis

Multiple bias analysis techniques are an extension of basic sensitivity analyses[40,53] which allow investigators to address multiple non-independent threats to a study's validity in one analysis[30]. This analysis employed Monte-Carlo based, probabilistic, multiple bias-analysis techniques[30,40,42,44,54-57] to evaluate the influence of selection bias and misclassification in the three selected studies of abortion related mortality. While the prior distributions chosen for each of the bias parameters (selection and misclassification) differed across studies based on data limitations, geographic location, and study-specific strategies employed to minimize selection bias, a common analysis plan was followed for the analysis of all three studies. The analysis plan, described in detail below, is intended as guide for the implementation of the following eight steps: **Step 1.** Specify probability distributions for the selection probabilities of abortion related deaths and non-abortion related deaths in each study. **Step 2.** Specify probability distributions for the sensitivity and specificity of classifying abortion related deaths for each study. **Step 3**. Using crude data from each of the studies, calculate the proportion of abortion related deaths in each study. **Step 4.** Construct 95% confidence intervals for the reported proportion of abortion related deaths for each study. **Step 5.** Adjust the reported proportion of abortion related deaths for selection bias in each study. **Step 6.** Using the selection-bias adjusted proportion of abortion related deaths, subsequently adjust for misclassification in each study. **Step 7.** Incorporate random error into the adjusted estimates for each study and construct a range of possible values for the proportion of abortion related deaths adjusted for selection bias, misclassification, and random error for each study. **Step 8.** Model 50,000 Monte Carlo simulation trials for each simulation experiment under different probability distribution scenarios; twenty-one scenarios in total.

Analysis Plan

All statistical analyses were conducted using R (R Development Core Team (2011). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/).

Step 1:

We specified probability distributions (in essence Bayesian Prior distributions) [30] for the selection probabilities of abortion related deaths and non-abortion related deaths in each study. Because internal validation studies were not conducted in any of the studies chosen, other sources of data were relied upon to determine the potential impact of selection bias. Following the techniques used to define prior distributions in much of the multiple bias literature[30,57,58], two sources of information were used to specify the probability distributions: 1) data from validation studies of maternal mortality conducted in similar populations, 2) adjustment factors commonly used in the demographic literature to adjust for underestimation of maternal death in studies of maternal mortality and abortion related mortality. While these two sources of probability distributions are imperfect proxies for the real selection probabilities in each of the studies of interest, the assumption is made that selection bias performs similarly in studies in the same region of the world, and therefore, by constructing probability distributions of a range of possible values of selection bias, we can explicitly state the range of selection bias that we are assuming, and model what the data would have looked like given a random sampling of those possible values. For each of the three studies, we performed an online literature search of PubMed, JSTOR, and Popline databases for all English-language studies of maternal mortality, abortion related mortality, or unsafe abortion that had been conducted in the country where the study was performed. If fewer than 2 studies could be found, the search was expanded to the geographic region where the study was performed. The search sought to identify articles that provided an estimate of the proportion of maternal deaths or (preferably) abortion related deaths that had been captured by their study through some form of validation (in the case of facility-based studies, most often this would be validation against official records; in the case of verbal-autopsy studies, validation against official records, or a combination of data sources). In April of 2012, we performed a search of the databases for English-language studies containing the following key-words: *abortion, induced abortion, unsafe abortion, maternal mortality, maternal death, pregnancy related death, cause of death, verbal autopsy*, *and the country (or region) of interest.* The reviewer evaluated study titles and abstracts to select articles for full-text review. The references of articles were also reviewed for potential additional resources. Studies were included for full-text review if they provided any measure of validation for the selection probabilities of maternal deaths overall, or abortion-related deaths specifically, or among facility-based studies, any study that included the proportion of records extracted. Studies were also included if they provided population-level estimates of maternal death and/or abortion related deaths that were arrived at through demographic algorithms which used some adjustment factor for missing data. We excluded articles that provided estimates of selection probabilities based on other

sources of data. Trapezoidal distributions of the range of possible values for the selection probabilities of abortion related deaths and non-abortion related deaths were modeled. Trapezoidal distributions are the most commonly employed distributions in the multiple-bias analysis literature[30,57] as they allow for the specification of the range of most likely values (between mode 1 and mode 2) and the range of all possible values (between minimum and maximum specified values). It has been repeatedly demonstrated that the shape of the distribution (normal, trapezoidal, triangular, etc…) makes no impact on the final result[30]. For the trapezoidal distribution, the lowest and highest reported selection probabilities or adjustment factors for abortion related mortality in each country/region were selected as the upper (maximum) and lower (minimum) bounds of the probability distribution for abortion related mortality in each study, and the lowest and highest reported selection probabilities or adjustment factors for overall maternal mortality in each country/region were used as measures of the selection probabilities of non-abortion related deaths and selected as the upper and lower bounds of the probability distribution for non-abortion related mortality in each study. For example, the literature search for study A found the lowest reported selection probability to be 0.02 (i.e. only 2% of potential abortion-related deaths were missed by the study) and the highest reported selection probability to be 0.5 (i.e 50% of potential abortion-related deaths were missed by the study).

The two modal values were the most commonly reported selection probabilities or adjustment factors, or, if only one probability emerged as most common, that probability was selected as the halfway point between the two modal values. Again, for study A, the most commonly reported selection factors were 0.2 (i.e. 20% of abortion-related deaths were missed) and 0.25 (i.e. 25% of abortion-related deaths were missed). Three iterations of trapezoidal modes were modeled for each selection probability, with varying widths between the modal values (narrow, medium, and wide), to examine/assess the implications of modal value selection on the final results.

Step 2:

We again specified probability distributions (analogous to Bayesian Prior distributions) for the sensitivity and specificity of classifying abortion related deaths for each study. As in Step 1, no internal validation studies were conducted, which necessitated the reliance on external data sources to determine the sensitivity and specificity of classification of abortion related death. As above, two sources of information were used to specify these probability distributions: 1) Data from validation studies of verbal autopsy algorithms conducted in the same country or in similar populations, 2) Data from validation studies conducted in the same country (or in similar populations) of cause of death classification from clinical case notes against autopsy diagnoses. While these two sources of data are again imperfect, there is a substantial validation literature testing the sensitivity and specificity of cause of death classification in different parts of the world that was used to inform our choices of bounds for the range of possible values of sensitivity and specificity.

The results of the online literature search described in step 5 were used to identify studies that provided an estimate of the sensitivity and specificity of the classification of abortion related deaths in either facility-based studies or in verbal autopsy studies. As

before, if fewer than 2 studies could be found, the search was expanded to the geographic region where the study was performed. The reviewer again evaluated study titles and abstracts to select articles for full-text review. The references of articles were also reviewed for potential additional resources. Studies were included for full-text review if they provided a measure of sensitivity and specificity of abortion related deaths. Because no studies identified the sensitivity and specificity of abortion related death classification, because the test characteristics did not differ greatly across study or geographic region, and because the abortion-measurement literature broadly supports the idea that sensitivity and specificity of abortion related conditions in countries where abortion is illegal does not vary widely[28], the same probability distributions of sensitivity and specificity were used for each study.

Again trapezoidal distributions were employed to model the range of possible values for sensitivity and specificity of cause of death classification. The lowest and highest reported sensitivities and specificities for abortion related mortality were selected as the upper and lower bounds of the probability distributions. The two modal values were chosen as representative of the most commonly reported selection probabilities or adjustment factors. Again, three iterations of trapezoidal modes were modeled for each parameter (sensitivity and specificity), with varying widths between the modal values (narrow, medium, wide) to test the implications of modal value selection on the final results.

In all, twenty-one possible combinations of varying widths of selection probabilities and classification distributions were tested for each study. Table 1, Table 2, and Table 3 present the specified bounds of the trapezoidal distributions modeled for each scenario tested in each of the studies A, B, and C respectively.

Step 3:

Using crude data from each of the studies, we used the following formula to calculate the proportion of abortion related deaths in each study:

$\mathbf{Y_0}= \frac{X_{0\,ARD}}{Total_{MD}}$ where $\mathbf{Y_0}$ is the proportion of observed abortion related deaths (ARD)

X_{0ARD} is the number of abortion related deaths identified by the study and $Total_{MD}$ is the total number of maternal deaths identified by the study.

Step 4:

Given that none of the studies in the systematic review presented any measure of random error around their point estimates, we constructed 95% confidence intervals for the reported proportion of abortion related deaths for each study. We used the following formula to construct a probability distribution and a 95% confidence interval of a proportion:

1. $SE=sqrt(Y_0*(1-Y_0)/(Total_{MD}))$, where SE is the standard error of Y_0, and Y_0 is the proportion observed abortion related deaths in the study.

2. $95\%\ CI= Y_0 \pm$ SE

Step 5:

Following conventional practice, we adjusted the proportion of abortion related deaths following the order in which the biases occurred[53]. Given that subjects must, by necessity, be selected into any study before misclassification can occur, we adjusted for selection bias first. We used the following formulae to adjust for selection bias in the study:

1. $\mathbf{X_{1ARD}} = \left(\frac{X_{0\,ARD}}{W_1}\right)$ where $\boldsymbol{X_{1ARD}}$ is the number of abortion related deaths adjusted for selection bias, $\boldsymbol{X_{0ARD}}$ is the number of abortion related deaths identified by the study, and where $\boldsymbol{W_1}$ is the a priori specified trapezoidal distribution of all possible values for the selection probability for abortion related deaths.

2. $\mathbf{X_{1NARD}} = \left(\frac{X_{0\,NARD}}{W_2}\right)$ where $\boldsymbol{X_{1NARD}}$ is the number of non-abortion related maternal deaths adjusted for selection bias**,** $\boldsymbol{X_{0NARD}}$ is the number of non abortion related maternal deaths identified by the study, and where $\boldsymbol{W_2}$ is the selection probability for non-abortion related maternal deaths.

3. $\mathbf{Y_1} = \dfrac{\left(\frac{X_{0\,ARD}}{W_1}\right)}{\left(\frac{X_{0\,ARD}}{W_1} + \frac{X_{0\,NARD}}{W_2}\right)}$ where $\mathbf{Y_1}$ is the proportion of abortion related deaths observed in the study adjusted for selection bias, and other notation is as above.

Step 6:

Given that misclassification can only occur among subjects selected into any study, we therefore used $\boldsymbol{Y_1}$ (the proportion of abortion related deaths observed in the study adjusted for selection bias) as the baseline for adjustment for misclassification. We used the following formulae to adjust for misclassification in the study:

1. $\mathbf{X_{2ARD}} = \left[\left(X_{1ARD} * W_3\right) + \left(X_{1NARD} - X_{1NARD} * W_4\right)\right]$ where $\boldsymbol{X_{2ARD}}$ is the number of abortion related deaths adjusted for selection bias and misclassification, $\boldsymbol{X_{1ARD}}$ is the number of abortion related deaths adjusted for selection bias and $\boldsymbol{X_{1NARD}}$ is the number of non abortion related maternal deaths adjusted for selection bias, and where $\mathbf{W_3}$ is the sensitivity of classification of abortion-related death and $\boldsymbol{W_4}$ is the specificity of classification of abortion related death.

2. $\mathbf{X_{2NARD}} = \left[\left(X_{1NARD} * W_3\right) + (X_{1ARD} - \left(X_{1ARD} * W_4\right)\right]$ where $\boldsymbol{X_{2ARD}}$ is the number of non-abortion related deaths adjusted for selection bias and misclassification, $\boldsymbol{X_{1ARD}}$ is the number of abortion related deaths adjusted for selection bias and $\boldsymbol{X_{1NARD}}$ is the number of non abortion related maternal deaths adjusted for selection bias, where

$\mathbf{W_3}$ is the sensitivity of classification of abortion related death and $\boldsymbol{W_4}$ is the specificity of classification of abortion related death.

3. $\mathbf{Y_2} = \frac{X_{2ARD}}{X_{2ARD} + X_{2NARD}}$ where $\boldsymbol{Y_2}$ is the proportion of abortion related deaths adjusted for selection bias and misclassification, and where $\boldsymbol{X_{2ARD}}$ is the number of abortion related deaths adjusted for selection bias and misclassification and $\boldsymbol{X_{2NARD}}$ is the number of non abortion related maternal deaths adjusted for selection bias and misclassification.

Step 7:

After adjusting for both sources of bias (selection bias and misclassification) random error must be incorporated into the new estimate. Using the same formulae that were employed in Step 1, we accounted for random error, and constructed the range of possible values for proportion of abortion related deaths for each study. We used the following formula to construct a probability distribution and a range of possible values for the proportion:

1. $\boldsymbol{SE=sqrt(Y_2*(1-Y_2)/(Total_{MD}))}$, where $\boldsymbol{SE}$ is the standard error of $\boldsymbol{Y_2}$, and $\boldsymbol{Y_2}$ is the proportion of observed abortion related deaths in the study adjusted for selection bias and misclassification.

2. $\boldsymbol{95\%\ CI = Y_2 \pm\ SE.}$

Step 8.

Twenty-one different simulation experiments were modeled for each study. The trapezoidal distributions used for each scenario are presented in Table 1 (*Study A*), Table 2 (*Study B*), and Table 3 (*Study C*). 50,000 Monte Carlo simulation trials were run for each simulation experiment.

Results

Table 4, Table 5, and Table 6 present the results of multiple bias analysis for adjustment of selection bias, misclassification, and incorporation of random error for *Studies A, B,* and *C*, respectively. For each of the studies, the proportion of abortion related deaths (median) increased substantially after multiple bias analysis.
Study A reported a median of 0.007 (less than 1% abortion related maternal deaths). After adjustment for selection bias under three distribution scenarios, the median increased, on average, to 0.023. After adjustment for selection bias and misclassification, the median increased, on average, to 0.066. After quantifying random error in the multiple bias analysis, the median was, on average, 0.06; nearly 9 times greater than the reported proportion of abortion related deaths. Had the authors of *Study A* reported a 95% confidence interval around their reported median, the range would have been: 0.001-0.023 (ratio of limits: 23.0). After adjustment for selection bias under three scenarios, the potential range widened to: 0.011-0.088 (average ratio of limits: 7.1). After adjustment

for selection bias and misclassification under 9 scenarios, the potential range was: 0.029-0.121 (average ratio of limits: 3.7). After including random error in the multiple bias analysis of selection bias and misclassification, the potential range widened further to: 0.007-0.157 (average ratio of limits: 21.4).

Study B reported a median of 0.256 (25.6% of maternal deaths were abortion related). After adjustment for selection bias under three distribution scenarios, the median increased, on average, to 0.370. After adjustment for selection bias and misclassification, the median was, on average, 0.306. After including random error into the multiple bias analysis, the median was, on average, 0.308; approximately 20% greater than the reported proportion of abortion related deaths. Had the authors of *Study B* reported a 95% confidence interval around their reported median, the range would have been: 0.196-0.316 (ratio of limits: 1.6). After adjustment for selection bias under three scenarios, the potential range widened to: 0.242-0.550 (average ratio of limits: 2.2). After adjustment for selection bias and misclassification under 9 scenarios, the potential range was: 0.203-0.458 (average ratio of limits: 2.1). After including random error in the multiple bias analysis of selection bias and misclassification, the potential range widened further to: 0.169-0.485 (average ratio of limits: 2.4).

Study C reported a median of 0.063 (6.3% of maternal deaths were abortion related). After adjustment for selection bias under three distribution scenarios, the median increased, on average, to 0.099. After adjustment for selection bias and misclassification, the median increased, on average, 0.119. After including random error in the multiple bias analysis, the median was, on average, 0.118; an increase of approximately 90% over the reported proportion of abortion related deaths. Had the authors of *Study C* reported a 95% confidence interval around their reported median, the range would have been: 0.045-0.080 (ratio of limits: 1.8). After adjustment for selection bias under three scenarios, the potential range widened to: 0.057-0.179 (average ratio of limits: 3.0). After adjustment for selection bias and misclassification under 9 scenarios, the potential range was: 0.069-0.188 (average ratio of limits: 2.5). After including random error in the multiple bias analysis of selection bias and misclassification, the potential range widened further to: 0.060-0.200 (average ratio of limits: 3.1). Figures 2, 3, and 4 present a graphical depiction of the results of multiple bias analysis for *Study C*, under the medium width distribution scenarios. A full set of graphical depictions for all three studies can be found in Appendix 2.

Discussion

In this paper we applied the multiple bias analysis framework to estimates of abortion related mortality and performed multiple bias analyses (adjusting for selection bias and misclassification, and integrating random error) on estimates of the proportion of abortion related mortality reported by three different studies. We believe that both selection bias and misclassification were present in all three studies analyzed, though the impact varied by study location, quality, and data collection methods. However, because no internal validation studies were conducted in any of the studies, we generated the prior probability distributions for selection bias and misclassification from existing validation studies, and commonly employed demographic adjustment factors. After thorough review of the existing validation studies, and other literature, it was determined that selection bias was

likely to vary substantially by study site, but that misclassification of abortion related deaths in settings where abortion is illegal, was unlikely to vary by study site. Despite our best efforts to accurately represent the potential range of the extent of selection bias and misclassification in each of the studies, we could not be certain about the extent of systematic error, nor could we be certain of the magnitude or direction of the resulting bias. Consequently, we developed 21 different scenarios for each study, exploring all possible combinations of prior probability distributions for each study in order to identify trends in the generated bias-adjusted estimates for abortion related mortality.

Our finding in all three studies, under all twenty-one scenarios of multiple bias analysis, that the median proportion of abortion related deaths increased (in some scenarios quite substantially) provides quantitative evidence that systematic error, specifically selection bias and misclassification, may indeed result in estimates of the proportion of abortion related maternal deaths that underestimate the true proportion of abortion related maternal deaths. For *Study A*, which initially found less than 1% of maternal deaths to be abortion-related, the proportion of abortion-related mortality was underestimated by a factor of eight; for *Study C*, which initially found approximately 6% of maternal deaths to be abortion-related, the proportion of abortion related deaths was underestimated by a factor of approximately two; and for *Study B*, which found nearly 25% of maternal deaths to be abortion-related, the proportion of abortion the proportion of abortion related deaths was underestimated by a factor of 1.2. It is unsurprising that the underestimation of abortion related deaths decreases as the proportion of abortion-related deaths initially identified by the study increases, suggesting that abortion related deaths are likely to cause more maternal deaths than many studies have been able to identify. . The decreasing levels of underestimation associated with higher levels of observed abortion related mortality may also speak to the challenges in identification of opposing biases. If, for example, studies conducted in tertiary facilities, as in *Study B*, indeed miss women who die from abortion related causes without seeking care in facilities, but also identify a larger proportion of abortion-related deaths than would be seen in the general population because they treat the most serious abortion-related complications, the resulting biases, acting in opposite directions, would make it nearly impossible to determine the magnitude of each bias, but would make the net effect of the biases smaller than.

These findings have broad reaching implications for the way we understand the distribution of cause of maternal death in a range of scenarios. If, as our data suggest, abortion related deaths account for a larger proportion of maternal deaths than previously thought, these methods can be used to more accurately determine the range of potential burden of abortion related mortality in local and country specific contexts, and can also be used to help policy makers and program planners target funds towards increasing access to family planning and safe abortion services at the community level, and, where abortion remains illegal, focusing on providing widespread access to comprehensive post abortion care. Such policies and programs will be fundamental to addressing the issue of mortality resulting from unsafe abortion. Our finding that, across studies and across scenarios, the range of possible values of the proportion of abortion related deaths increased with multiple bias analysis is further evidence that the current estimates of abortion related mortality are not precise, and that those ranges vary widely by study site. This finding serves as a reminder to all investigators interested in quantifying the

proportion of abortion related deaths in any setting, that, given the limitations of our data, we should report the observed proportion of abortion related deaths along with their appropriate confidence intervals in order to ensure readers are aware of the imprecision and potentially biased nature of our estimates.

Multiple bias analysis provides authors with a set of mathematical and statistical tools to estimate the effect of biases across a range of plausible magnitudes on the parameters estimated from the study data. In circumstances where systematic error is known to be present, some form of bias analysis should not only be considered a necessary analytic step, it can also serve as a useful framework to help readers of the epidemiologic literature interpret results vis-á-vis the magnitude and likelihood of potential biases. When authors report the results of traditional epidemiologic analyses, they traditionally do not quantify the role of bias in those results, implicitly making the assumption that biases do not exist or are unlikely to change their results. Multiple bias analysis allows authors to exchange those implicit assumptions for explicit assumptions through the quantification of selection bias and sensitivity/specificity.

Indeed, bias analyses have been criticized for their subjective nature—any prior specification of bias is subject to the authors' interpretation of validation studies in similar populations and expert knowledge, and not the "truth". However, bias analyses are far better than ignoring bias. The assumptions are clearly stated, and the analysis can be easily repeated under different scenarios with different assumptions. When no bias analysis is conducted, the reader relies on the authors' qualitative assessment of biases, or, is simply left on her own to surmise where systematic error might exist and how it might affect the study result.

The multiple bias analysis framework provides a relatively simple, quantitative strategy for assessing systematic error and resulting bias in any epidemiologic study. While this paper presents a blueprint for multiple bias analysis of a proportion, the method can be applied to the analysis of multiple biases in more traditional exposure-disease relationships, and regression analyses as well. Multiple bias analysis is particularly applicable to the field of global reproductive health where issues of selection factors, willingness to participate in studies, misreporting, and underreporting of sensitive behaviors have long been acknowledged as obstacles to the collection of high quality data. With some fairly simple steps, reporting results of multiple bias analyses in estimates of abortion related mortality, predictors of unsafe abortion, and other abortion related reproductive health questions that suffer from similar biases, would not only improve reporting practices in the field, but would provide a guide for readers to understand the biases that exist in the data and how those biases might impact the observed data. It would also provide policymakers with a more accurate understanding of the potential impact of policies that target the underlying causes of unsafe abortion and abortion related mortality.

Tables and Figures

Table 1 Descriptions of trapezoidal probability distributions used for multiple-bias analysis of Study A

Study	Scenario	W_1*	W_2*	W_3*	W_4*	RE
Study A	1	0.02, 0.2, 0.25, 0.5	0.5, 0.7, 0.8, 1.0	None	None	None
	2	0.02, 0.17, 0.3, 0.5	0.5, 0.65, 0.85, 1.0	None	None	None
	3	0.02, 0.12, 0.35, 0.5	0.5, 0.6, 0.9, 1.0	None	None	None
	4	0.02, 0.2, 0.25, 0.5	0.5, 0.7, 0.8, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	None
	5	0.02, 0.2, 0.25, 0.5	0.5, 0.7, 0.8, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	None
	6	0.02, 0.2, 0.25, 0.5	0.5, 0.7, 0.8, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	None
	7	0.02, 0.17, 0.3, 0.5	0.5, 0.65, 0.85, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	None
	8	0.02, 0.17, 0.3, 0.5	0.5, 0.65, 0.85, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	None
	9	0.02, 0.17, 0.3, 0.5	0.5, 0.65, 0.85, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	None
	10	0.02, 0.12, 0.35, 0.5	0.5, 0.6, 0.9, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	None
	11	0.02, 0.12, 0.35, 0.5	0.5, 0.6, 0.9, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	None
	12	0.02, 0.12, 0.35, 0.5	0.5, 0.6, 0.9, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	None
	13	0.02, 0.2, 0.25, 0.5	0.5, 0.7, 0.8, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	Standard
	14	0.02, 0.2, 0.25, 0.5	0.5, 0.7, 0.8, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	Standard
	15	0.02, 0.2, 0.25, 0.5	0.5, 0.7, 0.8, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	Standard
	16	0.02, 0.17, 0.3, 0.5	0.5, 0.65, 0.85, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	Standard
	17	0.02, 0.17, 0.3, 0.5	0.5, 0.65, 0.85, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	Standard
	18	0.02, 0.17, 0.3, 0.5	0.5, 0.65, 0.85, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	Standard
	19	0.02, 0.12, 0.35, 0.5	0.5, 0.6, 0.9, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	Standard
	20	0.02, 0.12, 0.35, 0.5	0.5, 0.6, 0.9, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	Standard
	21	0.02, 0.12, 0.35, 0.5	0.5, 0.6, 0.9, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	Standard

* Trapezoidal distribution (minimum value, mode 1 value, mode 2 value, maximum value).
W_1: Selection probability for abortion related deaths
W_2: Selection probability for non-abortion related deaths
W_3: Sensitivity of cause of death classification
W_4: Specificity of cause of death classification
RE: Random Error

Table 2 Descriptions of trapezoidal probability distributions used for multiple-bias analysis of Study B

Study	Scenario	W_1*	W_2*	W_3*	W_4*	RE
Study B	1	0.2, 0.34, 0.43, 0.78	0.5, 0.7, 0.8, 1.0			None
	2	0.2, 0.30, 0.50, 0.78	0.5, 0.65, 0.85, 1.0			None
	3	0.2, 0.24, 0.53, 0.78	0.5, 0.6, 0.9, 1.0			None
	4	0.2, 0.34, 0.43, 0.78	0.5, 0.7, 0.8, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	None
	5	0.2, 0.34, 0.43, 0.78	0.5, 0.7, 0.8, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	None
	6	0.2, 0.34, 0.43, 0.78	0.5, 0.7, 0.8, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	None
	7	0.2, 0.30, 0.50, 0.78	0.5, 0.65, 0.85, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	None
	8	0.2, 0.30, 0.50, 0.78	0.5, 0.65, 0.85, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	None
	9	0.2, 0.30, 0.50, 0.78	0.5, 0.65, 0.85, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	None
	10	0.2, 0.24, 0.53, 0.78	0.5, 0.6, 0.9, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	None
	11	0.2, 0.24, 0.53, 0.78	0.5, 0.6, 0.9, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	None
	12	0.2, 0.24, 0.53, 0.78	0.5, 0.6, 0.9, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	None
	13	0.2, 0.34, 0.43, 0.78	0.5, 0.7, 0.8, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	Standard
	14	0.2, 0.34, 0.43, 0.78	0.5, 0.7, 0.8, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	Standard
	15	0.2, 0.34, 0.43, 0.78	0.5, 0.7, 0.8, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	Standard
	7	0.2, 0.30, 0.50, 0.78	0.5, 0.65, 0.85, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	Standard
	8	0.2, 0.30, 0.50, 0.78	0.5, 0.65, 0.85, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	Standard
	9	0.2, 0.30, 0.50, 0.78	0.5, 0.65, 0.85, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	Standard
	10	0.2, 0.24, 0.53, 0.78	0.5, 0.6, 0.9, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	Standard
	11	0.2, 0.24, 0.53, 0.78	0.5, 0.6, 0.9, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	Standard
	12	0.2, 0.24, 0.53, 0.78	0.5, 0.6, 0.9, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	Standard

* Trapezoidal distribution (minimum value, mode 1 value, mode 2 value, maximum value).
W_1: Selection probability for abortion related deaths
W_2: Selection probability for non-abortion related deaths
W_3: Sensitivity of cause of death classification
W_4: Specificity of cause of death classification
RE: Random Error

Table 3 Descriptions of trapezoidal probability distributions used for multiple-bias analysis of Study C

Study	Scenario	W_1*	W_2*	W_3*	W_4*	RE
Study C	1	0.2, 0.4, 0.45, 0.8	0.5, 0.7, 0.8, 1.0			None
	2	0.2, 0.375, 0.425, 0.8	0.5, 0.65, 0.85, 1.0			None
	3	0.2, 0.30, 0.5, 0.8	0.5, 0.6, 0.9, 1			None
	4	0.2, 0.4, 0.45, 0.8	0.5, 0.7, 0.8, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	None
	5	0.2, 0.4, 0.45, 0.8	0.5, 0.7, 0.8, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	None
	6	0.2, 0.4, 0.45, 0.8	0.5, 0.7, 0.8, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	None
	7	0.2, 0.375, 0.425, 0.8	0.5, 0.65, 0.85, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	None
	8	0.2, 0.375, 0.425, 0.8	0.5, 0.65, 0.85, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	None
	9	0.2, 0.375, 0.425, 0.8	0.5, 0.65, 0.85, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	None
	10	0.2, 0.30, 0.5, 0.8	0.5, 0.6, 0.9, 1	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	None
	11	0.2, 0.30, 0.5, 0.8	0.5, 0.6, 0.9, 1	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	None
	12	0.2, 0.30, 0.5, 0.8	0.5, 0.6, 0.9, 1	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	None
	13	0.2, 0.4, 0.45, 0.8	0.5, 0.7, 0.8, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	Standard
	14	0.2, 0.4, 0.45, 0.8	0.5, 0.7, 0.8, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	Standard
	15	0.2, 0.4, 0.45, 0.8	0.5, 0.7, 0.8, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	Standard
	16	0.2, 0.375, 0.425, 0.8	0.5, 0.65, 0.85, 1.0	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	Standard
	17	0.2, 0.375, 0.425, 0.8	0.5, 0.65, 0.85, 1.0	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	Standard
	18	0.2, 0.375, 0.425, 0.8	0.5, 0.65, 0.85, 1.0	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	Standard
	19	0.2, 0.30, 0.5, 0.8	0.5, 0.6, 0.9, 1	0.6, 0.7, 0.8, 0.9	0.91, 0.95, 0.97, 0.99	Standard
	20	0.2, 0.30, 0.5, 0.8	0.5, 0.6, 0.9, 1	0.6, 0.65, 0.85, 0.9	0.91, 0.94, 0.98, 0.99	Standard
	21	0.2, 0.30, 0.5, 0.8	0.5, 0.6, 0.9, 1	0.6, 0.62, 0.82, 0.9	0.91, 0.92, 0.98, 0.99	Standard

* Trapezoidal distribution (minimum value, mode 1 value, mode 2 value, maximum value).
W_1: Selection probability for abortion related deaths
W_2: Selection probability for non-abortion related deaths
W_3: Sensitivity of cause of death classification
W_4: Specificity of cause of death classification
RE: Random Error

Table 4 Multiple bias analysis results for Study A: proportion of maternal deaths due to unsafe abortion adjusted for selection bias, misclassification, and random error, after 50,000 simulation trials per scenario.

Bias Model	Scenario (probability distribution/s)	Median	2.5, 97.5 percentiles	Ratio of limits
None (reported)	NA	0.007	0.007, 0.007	1.0
None (conventional, with estimate of precision)	NA	0.007	0.001, 0.023	23
Adjusted for selection only, no random error	1 (W_1&W_2 narrow)	0.024	0.012, 0.080	6.7
	2 (W_1&W_2 medium)	0.023	0.012, 0.081	6.8
	3 (W_1&W_2 wide)	0.023	0.011, 0.088	8.0
Adjusted for misclassification and selection bias, no random error	4 (W_1&W_2 narrow, W_3&W_4 narrow)	0.065	0.032, 0.111	3.5
	5 (W_1&W_2 narrow, W_3&W_4 medium)	0.070	0.031, 0.117	3.8
	6 (W_1&W_2 narrow, W_3&W_4 wide)	0.064	0.030, 0.111	3.7
	7 (W_1&W_2 medium, W_3&W_4 narrow)	0.065	0.032, 0.112	3.5
	8 (W_1&W_2 medium, W_3&W_4 medium)	0.069	0.031, 0.117	3.8
	9 (W_1&W_2 medium, W_3&W_4 wide)	0.064	0.030, 0.112	3.7
	10 (W_1&W_2 wide, W_3&W_4 narrow)	0.065	0.032, 0.116	3.6
	11 (W_1&W_2 wide, W_3&W_4 medium)	0.070	0.030, 0.121	4.0
	12 (W_1&W_2 wide, W_3&W_4 wide)	0.065	0.029, 0.116	4.0
Adjusted for misclassification and selection bias, random error included	13 (W_1&W_2 narrow, W_3&W_4 narrow)	0.061	0.008, 0.147	18.4
	14 (W_1&W_2 narrow, W_3&W_4 medium)	0.061	0.007, 0.154	22.0
	15 (W_1&W_2 narrow, W_3&W_4 wide)	0.059	0.007, 0.147	21.0
	16 (W_1&W_2 medium, W_3&W_4 narrow)	0.061	0.008, 0.147	18.4
	17 (W_1&W_2 medium, W_3&W_4 medium)	0.061	0.007, 0.154	22.0
	18 (W_1&W_2 medium, W_3&W_4 wide)	0.058	0.006, 0.148	24.7
	19 (W_1&W_2 wide, W_3&W_4 narrow)	0.061	0.008, 0.151	18.9
	20 (W_1&W_2 wide, W_3&W_4 medium)	0.062	0.007, 0.157	22.4
	21 (W_1&W_2 wide, W_3&W_4 wide)	0.058	0.006, 0.150	25.0

W_1: Selection probability for abortion related deaths
W_2: Selection probability for non-abortion related deaths
W_3: Sensitivity of cause of death classification
W_4: Specificity of cause of death classification

Table 5 Multiple bias analysis results for Study B: proportion of maternal deaths due to unsafe abortion adjusted for selection bias, misclassification, and random error, after 50,000 simulation trials per scenario.

Bias Model	Scenario (probability distribution/s)	Median	2.5, 97.5 percentiles	Ratio of limits
None (reported)	NA	0.256	0.256, 0.256	1.00
None (conventional, with estimate of precision)	NA	0.256	0.196, 0.316	1.61
Adjusted for misclassification only, no random error	1 (W_1&W_2 narrow)	0.369	0.248, 0.523	2.11
	2 (W_1&W_2 medium)	0.368	0.245, 0.530	2.16
	3 (W_1&W_2 wide)	0.372	0.242, 0.550	2.27
Adjusted for misclassification and selection bias, no random error	4 (W_1&W_2 narrow, W_3&W_4 narrow)	0.305	0.209, 0.431	2.06
	5 (W_1&W_2 narrow, W_3&W_4 medium)	0.308	0.210, 0.438	2.08
	6 (W_1&W_2 narrow, W_3&W_4 wide)	0.302	0.206, 0.432	2.10
	7 (W_1&W_2 medium, W_3&W_4 narrow)	0.305	0.207, 0.437	2.11
	8 (W_1&W_2 medium, W_3&W_4 medium)	0.306	0.207, 0.443	2.14
	9 (W_1&W_2 medium, W_3&W_4 wide)	0.302	0.204, 0.437	2.11
	10 (W_1&W_2 wide, W_3&W_4 narrow)	0.308	0.206, 0.452	2.19
	11 (W_1&W_2 wide, W_3&W_4 medium)	0.310	0.206, 0.458	2.22
	12 (W_1&W_2 wide, W_3&W_4 wide)	0.305	0.203, 0.452	1.96
Adjusted for misclassification and selection bias, random error included	13 (W_1&W_2 narrow, W_3&W_4 narrow)	0.307	0.175, 0.462	2.64
	14 (W_1&W_2 narrow, W_3&W_4 medium)	0.310	0.176, 0.469	2.66
	15 (W_1&W_2 narrow, W_3&W_4 wide)	0.304	0.173, 0.461	2.66
	16 (W_1&W_2 medium, W_3&W_4 narrow)	0.307	0.174, 0.467	2.68
	17 (W_1&W_2 medium, W_3&W_4 medium)	0.309	0.173, 0.473	2.78
	18 (W_1&W_2 medium, W_3&W_4 wide)	0.304	0.170, 0.466	2.74
	19 (W_1&W_2 wide, W_3&W_4 narrow)	0.311	0.173, 0.480	2.77
	20 (W_1&W_2 wide, W_3&W_4 medium)	0.313	0.172, 0.485	2.81
	21 (W_1&W_2 wide, W_3&W_4 wide)	0.308	0.169, 0.480	2.84

W_1: Selection probability for abortion related deaths
W_2: Selection probability for non-abortion related deaths
W_3: Sensitivity of cause of death classification
W_4: Specificity of cause of death classification

Table 6 Multiple bias analysis results for Study B: proportion of maternal deaths due to unsafe abortion adjusted for selection bias, misclassification, and random error, after 50,000 simulation trials per scenario.

Bias Model	Scenario (probability distribution/s)	Median	2.5, 97.5 percentiles	Ratio of limits
None (reported)	NA	0.063	0.063	1.00
None (conventional, with estimate of precision)	NA	0.063	0.045, 0.080	1.78
Adjusted for selection probability only, no random error	1 (W_1&W_2 narrow)	0.097	0.058, 0.169	2.91
	2 (W_1&W_2 medium)	0.099	0.058,0.172	2.96
	3 (W_1&W_2 wide)	0.100	0.057, 0.179	3.14
Adjusted for misclassification and selection bias, no random error	4 (W_1&W_2 narrow, W_3&W_4 narrow)	0.115	0.072, 0.175	2.43
	5 (W_1&W_2 narrow, W_3&W_4 medium)	0.118	0.070, 0.179	2.55
	6 (W_1&W_2 narrow, W_3&W_4 wide)	0.119	0.070, 0.178	2.54
	7 (W_1&W_2 medium, W_3&W_4 narrow)	0.117	0.073, 0.176	2.41
	8 (W_1&W_2 medium, W_3&W_4 medium)	0.121	0.071, 0.182	2.56
	9 (W_1&W_2 medium, W_3&W_4 wide)	0.120	0.070, 0.180	2.57
	10 (W_1&W_2 wide, W_3&W_4 narrow)	0.118	0.072, 0.181	2.51
	11 (W_1&W_2 wide, W_3&W_4 medium)	0.122	0.071, 0.188	2.65
	12 (W_1&W_2 wide, W_3&W_4 wide)	0.121	0.069, 0.186	2.70
Adjusted for misclassification and selection bias, random error included	13 (W_1&W_2 narrow, W_3&W_4 narrow)	0.115	0.062, 0.187	3.02
	14 (W_1&W_2 narrow, W_3&W_4 medium)	0.117	0.060, 0.191	3.18
	15 (W_1&W_2 narrow, W_3&W_4 wide)	0.117	0.060, 0.191	3.18
	16 (W_1&W_2 medium, W_3&W_4 narrow)	0.116	0.062, 0.188	3.03
	17 (W_1&W_2 medium, W_3&W_4 medium)	0.120	0.062, 0.195	3.14
	18 (W_1&W_2 medium, W_3&W_4 wide)	0.118	0.061, 0.193	3.16
	19 (W_1&W_2 wide, W_3&W_4 narrow)	0.117	0.062, 0.194	3.13
	20 (W_1&W_2 wide, W_3&W_4 medium)	0.121	0.062, 0.200	3.22
	21 (W_1&W_2 wide, W_3&W_4 wide)	0.119	0.060, 0.198	3.30

W_1: Selection probability for abortion related deaths
W_2: Selection probability for non-abortion related deaths
W_3: Sensitivity of cause of death classification
W_4: Specificity of cause of death classification

Figure 1: Framework for Systematic Error in Measurement of Abortion-Related Maternal Mortality

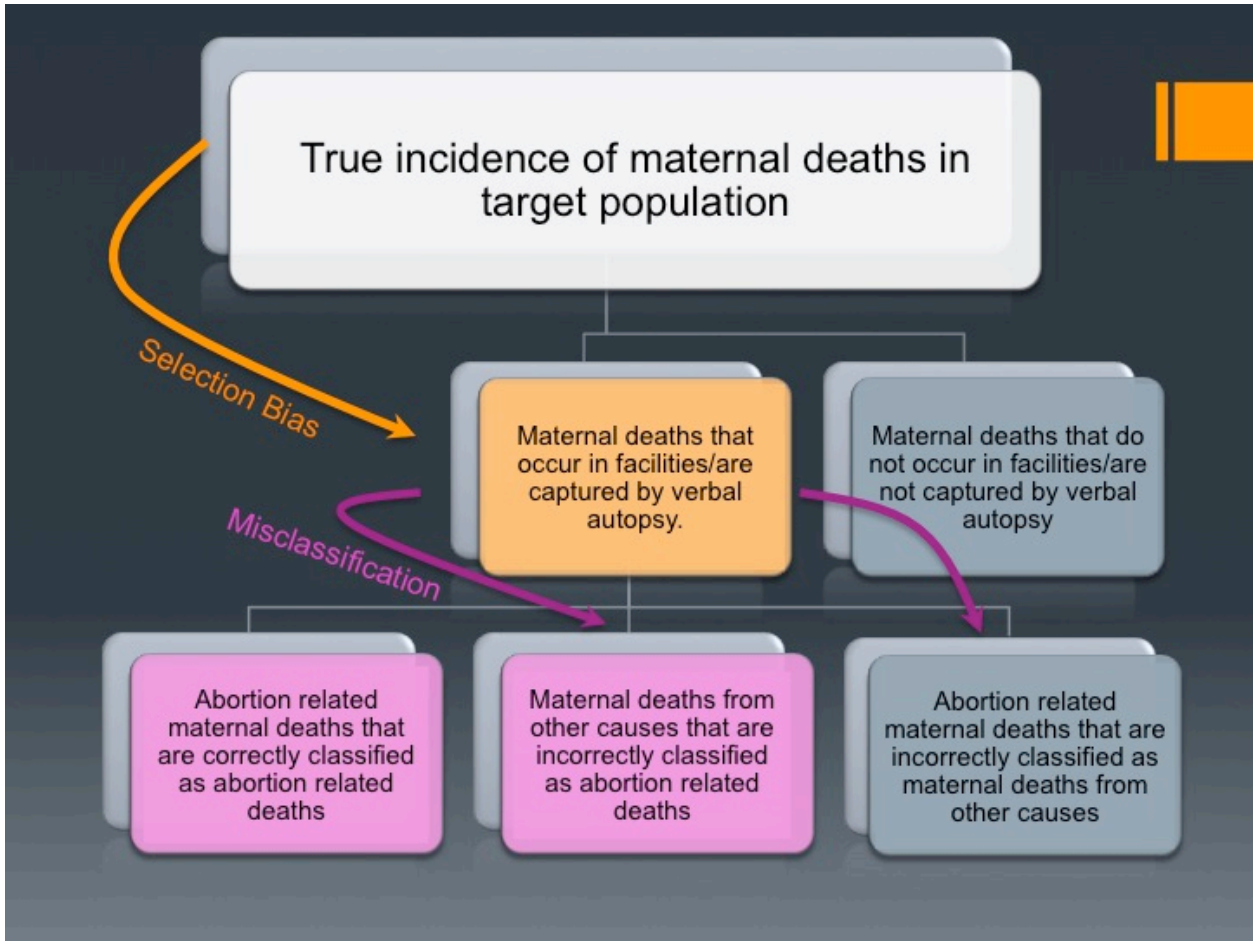


Figure 2: Proportion of abortion related deaths adjusted for selection bias (Study C)

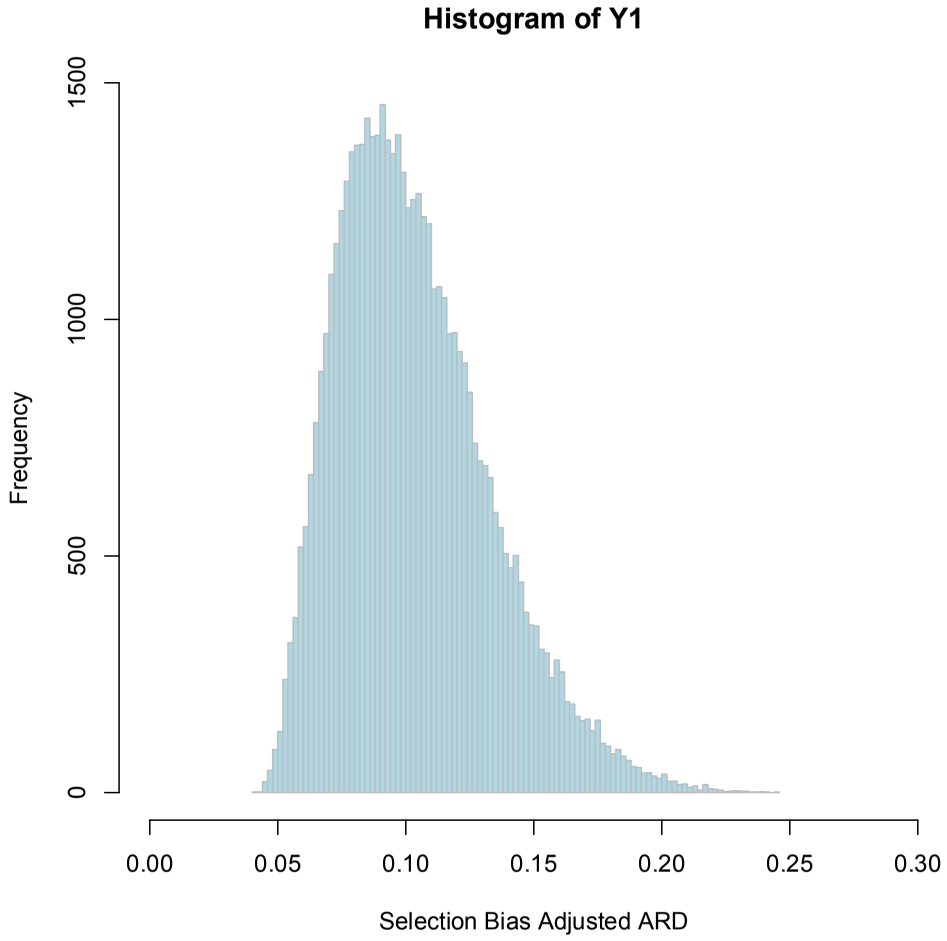


Figure 3: Proportion of abortion related deaths adjusted for selection bias and misclassification (Study C)

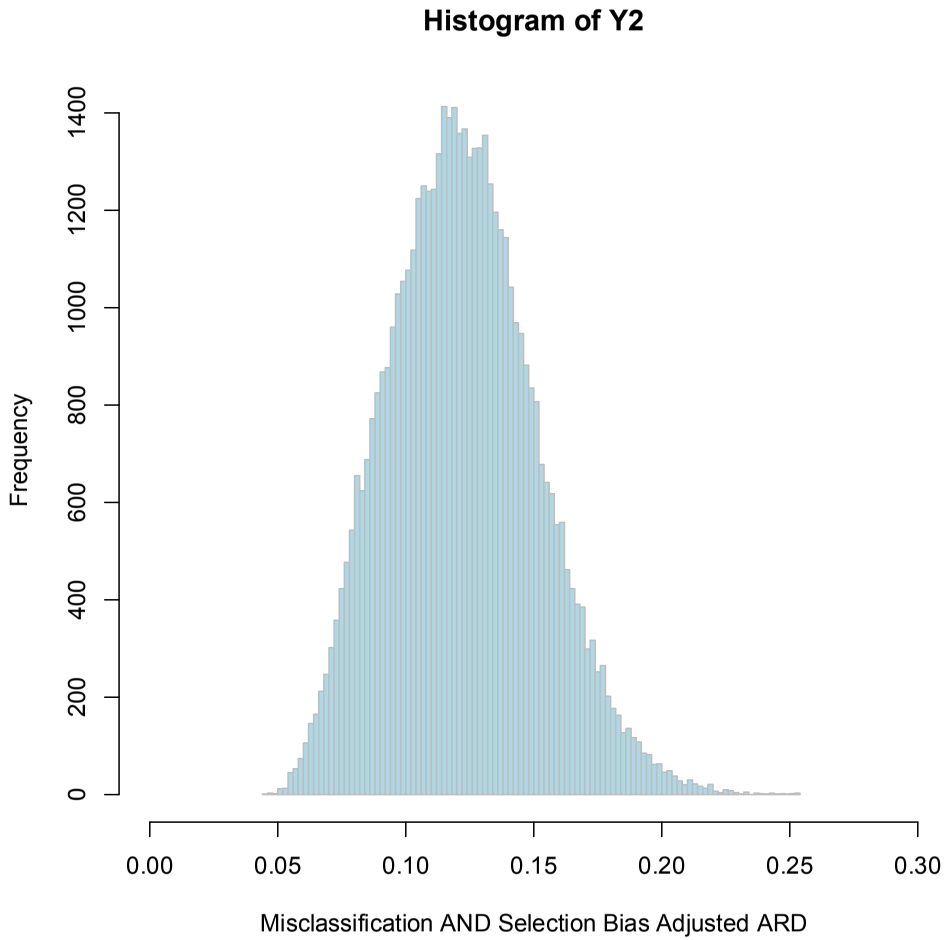
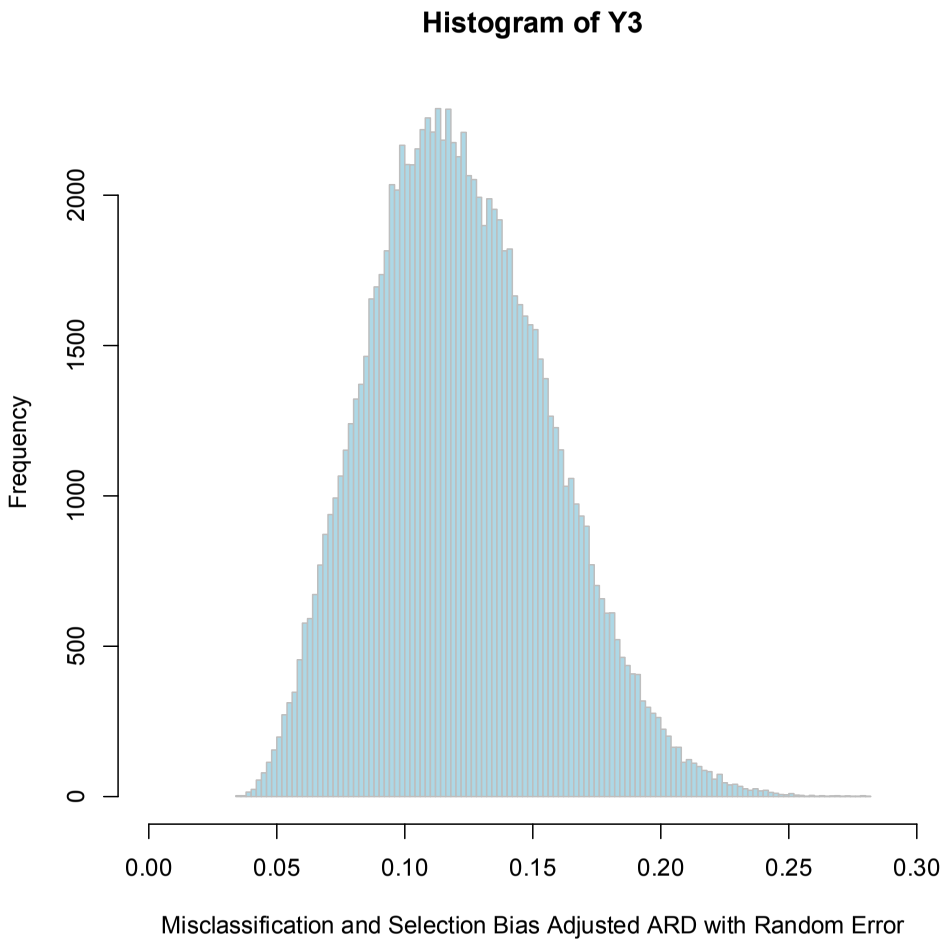


Figure 4: Proportion of abortion related deaths adjusted for selection bias, misclassification, and random error (Study C)



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Chapter 3

Post Abortion Care for Induced Abortion in Zanzibar, Tanzania: A Multiple Bias Analysis

Background

In Tanzania, as in much of Sub-Saharan Africa, abortion is prohibited except in cases in where the mother's life is in danger [1]. A woman in Tanzania can be imprisoned for up to seven years for attempting to induce abortion, and abortion providers can face a penalty of fourteen years in prison [2]. Contraceptive use in Tanzania is low; in the most recent Demographic and Health Survey (DHS) in 2010, only 27% of women reported using a modern method of family planning and unmet need for contraception is high; 25% of women in Tanzania have an unmet need for family planning [3]. According to the same DHS, in Zanzibar, a low-resource, predominantly Muslim archipelago in Tanzania, contraceptive prevalence is an even lower 12%, and unmet need for contraception is 34% [3].

Without reliable access to modern methods of contraception, unintended pregnancy is common in Tanzania [1]. Despite serious legal penalties for inducing abortion and social stigma surrounding the procedure, induced abortion is widely practiced in Tanzania (the estimated abortion rate is 39/1000 women) [4 5 -8]. Because abortion is illegal, however, most of the abortions performed in Tanzania are thought to be unsafe [9]. The WHO defines unsafe abortion as a procedure for terminating procedure for terminating an unwanted pregnancy either by persons lacking the necessary skills or in an environment lacking the minimal medical standards or both, and the consequences of unsafe abortion can be severe, and include hemorrhage, sepsis, chronic reproductive tract infections, infertility, and death [10,11].

The situation has a disproportionate impact on young, often unmarried women [1,12]. One study of four major public hospitals in Dar es Salaam, Tanzania in 2000 found that approximately over half (n = 197/360) of all complications from unsafe abortions were among women age 20 and below [13]. Young women in Tanzania may be at increased risk of unintended pregnancy due to a variety of factors including exposure to multiple sexual partners, lack of knowledge about contraception, transactional sex, and engaging in sex with older men [1,5,6]. Because pregnancies out of marriage are so highly stigmatized in Tanzania, young women who are unmarried in Tanzania may have a further elevated risk of unsafe abortion [1,5].

Unsafe abortion is one of the most preventable causes of maternal mortality and morbidity worldwide [14], and yet unsafe abortion now accounts for more than half of the worlds 20 million induced abortions each year [15]. Such high global incidence of unsafe abortion speaks to the need to better understand the determinants and consequences of unsafe abortion to support the creation of evidence based policies and interventions targeted at reducing unsafe abortion. Unfortunately, valid and accurate data can be difficult to capture.

Most data on unsafe abortion in Tanzania are collected from hospital-based registries of post-abortion complications identified through post-abortion care (PAC) services. PAC services are intended to provide care for women who experience complications from both induced and spontaneous abortions. Correctly distinguishing induced from spontaneous abortion-related complications can be challenging, as complications from induced and spontaneous abortions are often clinically indistinguishable [16]. Additionally, given the restrictive legal status of abortion and social stigma around abortion in Tanzania, women who have induced abortions may intentionally misclassify their reason for seeking PAC services as spontaneous abortions. Facility-based data are therefore likely to underestimate the true proportion of PAC cases that result from induced abortion and overestimate those resulting from spontaneous abortion. Data collected through the use of empathic interviewing techniques designed specifically for abortion

related research suggests that up to 60% of women presenting to hospitals in mainland Tanzania for post abortion [17] care (PAC) may have attempted to induce abortion [7,12,13,17].

Studies that seek to measure complications from induced abortion in settings where abortion is illegal or highly restricted ultimately seek to present valid, precise, and estimates of the underlying 'burden of disease'. To achieve these goals, attention must be given to the potential for both random and systematic error present in the data. Researchers have focused a great deal of attention on the development of accessible and interpretable methods for reporting random error, but the equally prevalent sources of systematic error (otherwise known as bias) in studies have received far less attention. Due to the necessity (ethical or practical) of non-randomized study designs, and imperfect measurement tools, some systematic error is present in most epidemiologic studies. Techniques for the quantitative assessment of systematic error have existed for decades [18], and range from simple sensitivity analyses [19] to complex Bayesian uncertainty analysis approaches [20]. These techniques, known broadly as bias analysis techniques, allow researchers to identify potential sources of systematic error in their data, use published literature and expert knowledge to assign probability distributions for the magnitude of that systematic error, and draw repeated random samples from those distributions to "correct" for the error that is likely to exist in their data. The technique ultimately produces a range and distribution of probable estimates for the desired measure (point estimates, odds ratios, risk ratios, etc) had no bias existed in the data to begin with. Applying such techniques to examine systematic error in studies is surely better than failing to recognize potential biases and presenting data we know to be biased.

To date there are no population-level data on induced abortion in Zanzibar, and very little is known about Zanzibari young women's experiences with sexuality or contraceptive use. One recent study, however, suggests that complications of unsafe abortion in mainland Tanzania comprise 3 of the leading 5 causes of hospital admissions [17], another report estimates that unsafe abortion in Tanzania contributes upwards of 17% of maternal mortality [4], and post abortion care has been recorded as the leading cause of admission to the gynecologic ward at Mnazi Mmoja Hospital, the sole tertiary care facility in Zanzibar. [21]

The purpose of our study was three fold: 1) to establish a "bias framework" for the identification of systematic error in hospital-based, post-abortion care data in settings where abortion is illegal, 2) employ the bias framework to examine the relationship between age and induced abortion among women seeking post abortion care services at Mnazi Mmoja Hospital in Zanzibar, Tanzania, and 3) employ multiple bias analysis techniques [20] to account for potential selection bias and misclassification in the data and generate a range of potential values for the association of age and induced abortion related PAC given different scenarios of bias.

Subjects and Methods

Setting:

Zanzibar's population of approximately 1.2 million is served by an established network of health facilities at the district and local level. The sole tertiary-level facility in Zanzibar is the Mnazi Mmoja Hospital.

Survey and Study Population:

Between July 2010 and November 2010, all women 15 years and older who presented to Mnazi Mmoja Hospital seeking care for an incomplete abortion (induced or spontaneous) between 6 a.m. and 6 p.m. Monday through Friday, were approached, after they had received care and were determined to be clinically stable, by hospital staff nurses and informed about this study. Approximately ninety percent of PAC cases arriving at Mnazi Mmoja Hospital during the study period (194 women) consented to participate and were enrolled in the study. Informed consent was given by the women, and IRB approval was granted by the Johns Hopkins School of Public Health. Zanzibari field workers – trained in the empathic interview methods [22] – conducted the one-hour interview with each participant in a private space adjacent to the gynecological ward. The Swahili-language questionnaire included questions about: basic demographic information; reproductive and contraceptive history; fertility intentions; and reproductive health decision-making.

The large majority of women seeking post abortion care at Mnazi Mmoja Hospital reported ambiguous or negative feelings about the pregnancy for which they were seeking care (158 out of 194 women). It has repeatedly been shown that women who experience wanted pregnancies behave in systematically different ways towards their pregnancies than women who experience unwanted pregnancies. For the purposes of this study, we were interested in women with unwanted pregnancies, and we restricted the analysis to those 158 women who reported that the pregnancy for which they were seeking post-abortion care had been unwanted. We defined feelings about pregnancy as unwanted if women reported negative or ambiguous feelings about their pregnancy.

Statistical Analysis:

Figure 1 represents the framework for potential systematic error in our study. The target population for this study has been defined as all women arriving at Mnazi Mmoja Hospital seeking post abortion care services who reported an unwanted pregnancy. If PAC cases resulting from induced abortion are more or less likely than PAC cases resulting from spontaneous abortion to arrive at Mnazi Mmoja Hospital during the interview window (Monday-Friday 6am-6pm) than outside of the interview window, bias will arise (eg, the proportion of PAC cases at the hospital resulting from induced abortion would differ from the proportion of PAC cases in the target population resulting from induced abortion). This bias can be identified as selection bias. Another form of selection bias could occur if women who had an induced abortion arrive at the hospital seeking post abortion care, but opt not to participate in the study. If PAC cases are more or less likely to be correctly classified as resulting from induced abortion than those resulting from spontaneous abortion, bias will again arise (eg, the sensitivity and specificity of PAC classification will differ for induced and spontaneous abortions, and the proportion of PAC cases resulting from induced abortion in the study population will differ from the true proportion in the enrolled population), this bias can be identified as misclassification.

Age and Induced Abortion

Multivariable logistic regression was conducted in order to examine the relationship between age and induced abortion among women experiencing an unwanted pregnancy in this study, controlling for other variables in the model. The covariates selected as potential confounders to be controlled for in our analyses were informed by data from epidemiologic research on unsafe abortion and post abortion care in Eastern African settings.

First, within most social structures, and indeed in Zanzibar, age (in years) is directly associated with years of education. For African women, small increases in education have repeatedly been shown to improve socio economic status [23, 24]. Second, the literature suggests that young girls and adolescents in sub-Saharan Africa may be less empowered than their older counterparts [25]. Strong evidence also exists that women's empowerment increases with increasing levels of education [24,26]. Additionally, lower socio-economic status has consistently been linked to lower levels of women's empowerment [24,27]. Third, low levels of empowerment and low levels education have both been identified as risk factors for unsafe abortion [14,28]. Finally, other, more difficult to measure, sociocultural factors at play in Zanzibar such as poverty, gender norms, religiosity, etc…may be associated with socioeconomic status, education, and empowerment.

Data

Exposure

The primary exposure of interest was age at time of presentation for PAC at Mnazi Mmoja Hospital. Age was measured in years, and was assessed by self-report.

Outcome

The outcome of interest was unsafe abortion. Because abortion is illegal in all of Tanzania except in the case where the mothers life is at risk, it is assumed that all induced abortions in our study population fit the WHO definition of unsafe abortion "a procedure for terminating an unwanted pregnancy by persons lacking the necessary skills, or in an environment lacking minimal medical standards, or both" [4]. Induced abortion was assessed by self-report.

Covariates

Education was assessed by self-report and was measured as years of continuous formal education. Empowerment was a composite measure created by the joint scores of two items, one: the Sexual Relationship Power Scale (SRPS) [29] that captures decision-making capacity, and the other, the DHS validated scale assessing tolerance of intimate partner violence [3]. A woman was considered to have a high level of empowerment if she reported that it was never acceptable for a man to hit or beat his wife/female partner AND if she reported that she was a primary household decision maker, either alone or with her husband. These household decisions included: 1) the woman's health matters, 2) large household purchases, 3) daily household

purchases, 4) whether she leaves the house 5) use of the woman's earnings, 5) use of partner's earnings. A woman was considered to have a low level of empowerment if she reported that someone other than she was not a primary household decision maker OR if she reported that it was ever acceptable for a man to hit or beat his wife/female partner.

Multivariable Logistic regression:

Multivariable logistic regression was performed using *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP. Utilizing the causal framework established by our DAG, we conducted bivariate logistic regression: $(\ln(odds(Y)) = \alpha + \beta 1_{Age} + \varepsilon$ to examine the total effect of age on unsafe abortion, and multivariate logistic regression: $(\ln(odds(Y)) = \alpha + \beta 1_{Age} + B2_{education} + B3_{empowerment} + \varepsilon$ to examine the direct effect of age on unsafe abortion, conditioning on education (continuous) and empowerment (categorical).

Simulation of multiple bias-corrected odds ratio

Employing the systematic error framework from the multiple bias analysis of the proportion of PAC cases resulting from unsafe abortion, we identified the likely sources of bias in our study to be, primarily outcome misclassification, and to a lesser extent, selection bias. Several assumptions were made in the implementation of multiple-bias analysis. First, to be consistent with the literature, we dichotomized the exposure variable (age), and defined exposure as: "below 20 years of age". Second, we assumed that the probability of misclassification of the outcome was non-differential with respect to the exposure, that is, the probability of being misclassified as having an induced vs. spontaneous abortion was the same for women of all ages. To assess the impact of selection bias and misclassification in our analysis of the effect of age on PAC resulting from induced abortion, we again utilized trapezoidal distributions to model the bias parameters. Trapezoidal distributions allow the specification of a range of potential values for each of the bias parameters, while placing more emphasis on the values between the two modes, and less emphasis on the values to the extremes of the two modes. For example, a trapezoidal distribution of sensitivity with a minimum value of 70%, modes of 75% and 85% and a maximum value of 90%, under repeated monte-carlo sampling, would be more likely to generate values of error probabilities between 15-25% and less likely to generate values between 25-30% and 10-15%. Because we do not have complete data on enrollment, because sensitivities and specificities are rarely known with certainty, and because the literature suggests a wide range of potential misclassification error [30] we modeled three parameters for the probability of selection into the study (narrow, medium, and wide) and three parameters for the sensitivity, and specificity of outcome classification (narrow, medium, and wide) (Table 1).

All multiple bias analyses were conducted in SAS (9), 2008, SAS Institute Inc., Cary, NC, USA, using the SENSMAC (SAS Macros) developed by Fox *et al* [20] to conduct probabilistic multiple bias analysis of the likely impact of selection bias into the study and misclassification of a dichotomous outcome. The program enabled us to randomly sample from each of the bias parameter distributions established for selection probability, sensitivity and specificity. Following the order in which the biases occurred [13], the analysis simulated the data that would have been observed in our study had selection into the study been unbiased, and had the outcome variable been correctly classified. For each of the three distributions (narrow, medium, wide) established for each of the three bias parameters (selection bias, sensitivity, and specificity), the

simulation was repeated 10,000 times in order to produce a median odds ratio and a simulation interval of potential odds ratios after accounting for selection bias, misclassification, and random error. The analysis accounted for random error by incorporating traditional 95% confidence intervals into each successive bias adjustment (i.e. the OR adjusted for selection bias alone also incorporates random error, and the OR adjusted for misclassification alone also incorporates random error, and the OR adjusted for selection bias and misclassification together also incorporates random error). One limitation of the current multiple bias analysis software for outcome misclassification, is its inability to include covariates in the bias analysis. Therefore, our multiple bias analysis of the relation between age and unsafe abortion is limited to analysis of the total (unadjusted) effect.

Results

Table 1 presents socio-demographic characteristics of our sample. The majority of women (54.4%) in the sample were between the ages of 21 and 30 years. Nearly all women interviewed reported that they were married (91.1%), and nearly half reported their occupation as "housewife" or "mother (47.5%). Just over half of the women interviewed (54.4%) reported being over twenty years of age when they first gave birth, but 36% reported being between the ages of 17 and twenty, and most women reported having been pregnant two times (56.3%). The majority of women reported having finished some secondary school (61.4%), and nearly the same proportion (62%) were determined to have a "high" level of empowerment. The large majority (95.6%) of women in our sample reported that they were seeking PAC for spontaneous abortion, and only 4.4%women reported that they were seeking PAC for an induced abortion.

Traditional Logistic Regression

Table 2 presents the results of our traditional bivariable and multivariable analyses. In unadjusted (bivariable) logistic regression models, with age as a continuous measure, we found a statistically significant decrease in the odds of experiencing an induced abortion (OR: 0.7. 95%CI: 0.53, 0.92) with each one-year increase in age. This association remained significant in multivariable logistic regression models conditioning on education and empowerment, where the odds of experiencing an induced abortion with each one-year increase in age decreased by thirty-one percent (OR: 0.69. 95%CI: 0.52, 0.92). When the variable age was dichotomized (<20 years of age=exposed, ≥20=unexposed), in bivariable analyses, the odds of induced abortion for women under the age of 20 were twenty five times greater than the odds of experiencing an induced abortion for women twenty or older (OR: 25.0. 95% CI: 2.9, 216.0), but with a wide confidence interval. In multivariable logistic regression, holding education and empowerment constant, the results were largely unchanged; odds of experiencing induced abortion for women under 20 was more than twenty six times greater (OR: 26.4. 95% CI: 3.0, 231.7), again with a wide confidence interval.

Multiple Bias Analysis of Logistic Regression

Table 4 presents the results of our multiple bias analyses, accounting for selection bias and outcome misclassification in the relation between age (as a dichotomous variable) and induced abortion. Comparisons were made between the distributions of odds ratios adjusted for selection bias and misclassification, and the distribution of the crude odds ratio observed in our study population. As the distribution of potential error widened, the median odds ratio, on average, was slightly lower. In addition, with wider potential error distributions, the distribution of possible odd ratio values widened to include substantially higher odds ratios. The median odds ratios generated from simulations adjusting for misclassification and selection bias and incorporating random error, were greater than the study's observed odds ratio in 89% of the scenarios, and were approximately equal to the study's observed odds ratio in 11% of the scenarios (Table 4). In 37% of scenarios, the median odds ratio was more than double that of the observed odds ratio. Under our assumptions about the probability distributions of selection bias and outcome misclassification parameters, and assuming that adjusting for potential confounders/mediators in multiple bias analyses would result in the same trends as were observed in traditional logistic regression (i.e. the results do not change significantly), Thus adjustment for selection bias and outcome misclassification in our study demonstrates that, indeed, women under the age of twenty years old have higher odds of PAC resulting from induced abortion than women over the age of twenty.

Discussion

The results from our multiple bias analysis, adjusting the observed odds ratios in our study population for selection bias and misclassification under a variety of probability distributions, indeed support our findings that being younger than twenty years of age significantly increases the odds of experiencing an unsafe abortion. Despite the small sample size of reported induced abortion, and the wide variability in our results because of the small cell sizes, these results give us more confidence in our initial findings because the trend of younger women having dramatically increased odds of unsafe abortion is upheld even after adjusting for multiple biases.

It is widely acknowledged that bias is present in the current estimates of PAC cases that result from induced abortion. Little, however, is known about the extent of those biases, and to date there have been no attempts to identify the specific biases in epidemiologic terms or to quantify the role of those errors in studies of PAC and induced abortion. Our framework for the examination of systematic error in the proportion of PAC cases resulting from induced abortion among women with unwanted pregnancies at Mnazi Mmoja Hospital in Zanzibar provides an example of how researchers can identify and potentially account for biases that exist in their studies.

The restrictive legal status of abortion in Tanzania leads women to use a wide array of methods to terminate unwanted pregnancies, most of them unsafe and potentially life threatening. Young women interviewed in a recent study reported using wood ashes (in a liquid solution), high doses of cloroquine (malaria treatment), laundry detergent (ingested or inserted vaginally), high doses of aspirin or other antibiotics, and a variety of medicinal plants and herbs taken orally or inserted in the vagina to induce abortion [5]. There is evidence that complications from unsafe abortion in mainland Tanzania are highly concentrated among women under the age of 20, thus, we were interested in examining the relationship between age and unsafe abortion in Zanzibar. Results from our traditional bivariable and multivariable analyses support the

hypothesis that young age (under 20 years old) is a risk factor for induced abortion among women with unintended pregnancies in Zanzibar. However, given our knowledge of the systematic error present in the reporting of induced abortion among our sample, the small sample size (7 reported induced abortions) and wide confidence intervals, it is difficult to draw conclusions from the traditional results unadjusted for selection bias and misclassification. Employing methods of multiple bias analysis allows us to better understand what our results would have been under different scenarios of bias.

The low proportion of PAC cases that were reported as having resulted from induced abortion in our study (4.5%) is substantially lower than would be expected in an East African context. It is unsurprising, given the legal status and stigma against abortion, that women in Zanzibar would be unlikely to admit having had an abortion. Additionally, because our study population was restricted to women experiencing an unwanted pregnancy, many of whom were young and poor, their unwillingness to disclose having induced abortion might have been compounded by additional social, economic, and relationship factors. In a study by Plummer *et al*, women who expressed a desire to terminate an unwanted pregnancy faced hostility from sexual partners, sexual exploitation from health practitioners, and broad reaching social stigma [5]. The low levels of reported induced abortion in our study likely reflects a widespread trend of women seeing post abortion care for complications of induced abortion but reporting them as complications from spontaneous abortion. The use of multiple bias analysis to "correct" for the misclassification resulting from such under-reporting, enables a better understanding of the impact of misclassification on our results. The results of our multiple bias analysis leads us to the conclusion that, had there been no misclassification present in our data, we would have seen an association between young age and induced abortion that was the same, or stronger,.

Our results add to a growing body of literature about the risks of unsafe abortion, especially for adolescent women in East Africa. In a study using empathic interview techniques to explore pregnancy experiences among teenage girls in Lusaka, Zambia most of the young women reported unstable current sexual relationships, very low levels of contraceptive knowledge, and relying primarily on unsafe abortion to "avoid" unwanted pregnancies. Young women reported being pressured to resort to unsafe abortion by family, partners (often extramarital), and a reproachful society in order to avoid the social consequences of being pregnant and unmarried [31]. Other studies in Tanzania have found that adolescent women experience more barriers to family planning services and reproductive health services in general, that put them at increased risk for unwanted pregnancies and complications from unsafe abortion [1,5,13]. The amassing evidence that adolescents disproportionately carry the burden of the consequences of unsafe abortion indeed is a call for better access to contraceptive services, youth-focused reproductive health services, and improved access to safe abortion where possible. It is also further reason for researchers to explore their studies through a framework of systematic error, identify where bias exists, and quantify how bias may be affecting study results. A more thorough analysis of bias enhance others' confidence in the results themselves.

Limitations

In order to adjust for selection bias and misclassification in our study, we established probability distributions (bias parameters) within which we believed the true magnitude of bias to exist. While those parameters were based on existing literature, and validation studies, where possible, it is possible that the bias parameters were too wide, too narrow, or altogether misspecified.

Were the bias parameters incorrectly specified, the results of our multiple bias analyses would, themselves, be biased. However, because we have explicitly identified the parameters used (Table 2), it would be relatively simple to recreate our analyses and test its sensitivity using a different set of parameters. While imperfect, specifying the assumptions made about the magnitude of the systematic error we believe to be present in our study is a vast improvement on the common practice of ignoring systematic error, or simply mentioning the possibility of its existence.

Additionally, the existing software does not allow us to examine multivariable relationships between the exposure and the outcome. While it is unlikely that the relationship effect we saw would be significantly different if adjusted for the two mediators (education and empowerment) as we did in traditional regression, the possibility nevertheless, exists.

Conclusion

In restrictive legal environments such as Tanzania, it will be increasingly important for abortion researchers to identify the potential sources of error in their data surrounding unsafe abortion, and when possible, quantify systematic error in order to instill confidence in the results we produce and encourage their use for true evidence based policy and program planning.

Table 1: Sociodemographic characteristics of women with unwanted pregnancies seeking post abortion care at Mnazi Mmoja Hospital

	%	N (158)
Age		
16-20	22.2%	35
21-25	25.3%	40
25-30	29.1%	46
31-35	8.2%	13
>35	15.2%	24
Relationship with father of index pregnancy		
Husband	91.1%	144
Fiance	1.9%	3
Boyfreind/lover	6.3%	10
Missing	0.6%	1
Education		
No education	8.2%	13
1-8 years	24.7%	39
secondary school	61.4%	97
college, diploma, certificate	3.2%	5
Missing	2.5%	4
Occupation		
Housewife/mother	47.5%	75
Farmer	4.4%	7
Small Business Merchant	17.1%	27
Office Worker	16.5%	26
Student	4.4%	7
Other	8.9%	14
Missing	1.3%	2
Empowerment Index		
High Empowerment	62.0%	98
Low Empowerment	43.0%	68
Number of Pregnancies		
1	31.6%	50
2	56.3%	89
3	11.4%	18
4	0.6%	1
Age at 1st birth		
Median (years of age)	--	22.0
<17 years	5.7%	9
17-20 years	36.7%	58
>20 years	54.4%	86
missing/don't know	3.2%	5
Reported Spontaneous Abortion	95.6%	151
Reported Induced Abortion	4.4%	7

Table 2 Descriptions of trapezoidal probability distributions used for multiple-bias analysis of the proportion of induced abortion related PAC cases

Model	W_1*	W_2*	W_3*	W_4*	W_4*	RE
1	0.95, 0.96, 0.97, 1.0	0.1, 0.14, 0.15, 0.2	0.91, 0.92, 0.93, 0.94	0.8, 0.85, 0.9, 0.95	0.8, 0.9, 0.95, 0.99	Standard
2	0.95, 0.96, 0.97, 1.0	0.1, 0.14, 0.15, 0.2	0.91, 0.92, 0.93, 0.94	0.7, 0.75, 0.9, 0.95	0.75, 0.9, 0.95, 0.99	Standard
3	0.95, 0.96, 0.97, 1.0	0.1, 0.14, 0.15, 0.2	0.91, 0.92, 0.93, 0.94	0.6, 0.7, 0.8, 0.95	0.7, 0.85, 0.9, 0.99	Standard
4	0.95, 0.96, 0.97, 1.0	0.1, 0.2, 0.24, 0.3	0.91, 0.93, 0.95, 0.97	0.8, 0.85, 0.9, 0.95	0.8, 0.9, 0.95, 0.99	Standard
5	0.95, 0.96, 0.97, 1.0	0.1, 0.2, 0.24, 0.3	0.91, 0.93, 0.95, 0.97	0.7, 0.75, 0.9, 0.95	0.75, 0.9, 0.95, 0.99	Standard
6	0.95, 0.96, 0.97, 1.0	0.1, 0.2, 0.24, 0.3	0.91, 0.93, 0.95, 0.97	0.6, 0.7, 0.8, 0.95	0.7, 0.85, 0.9, 0.99	Standard
7	0.95, 0.96, 0.97, 1.0	0.1, 0.3, 0.4, 0.5	0.91, 0.94, 0.96, 0.99	0.8, 0.85, 0.9, 0.95	0.8, 0.9, 0.95, 0.99	Standard
8	0.95, 0.96, 0.97, 1.0	0.1, 0.3, 0.4, 0.5	0.91, 0.94, 0.96, 0.99	0.7, 0.75, 0.9, 0.95	0.75, 0.9, 0.95, 0.99	Standard
9	0.95, 0.96, 0.97, 1.0	0.1, 0.3, 0.4, 0.5	0.91, 0.94, 0.96, 0.99	0.6, 0.7, 0.8, 0.95	0.7, 0.85, 0.9, 0.99	Standard
10	0.9, 0.92, 0.95, 1.0	0.1, 0.14, 0.15, 0.2	0.91, 0.92, 0.93, 0.94	0.8, 0.85, 0.9, 0.95	0.8, 0.9, 0.95, 0.99	Standard
11	0.9, 0.92, 0.95, 1.0	0.1, 0.14, 0.15, 0.2	0.91, 0.92, 0.93, 0.94	0.7, 0.75, 0.9, 0.95	0.75, 0.9, 0.95, 0.99	Standard
12	0.9, 0.92, 0.95, 1.0	0.1, 0.14, 0.15, 0.2	0.91, 0.92, 0.93, 0.94	0.6, 0.7, 0.8, 0.95	0.7, 0.85, 0.9, 0.99	Standard
13	0.9, 0.92, 0.95, 1.0	0.1, 0.2, 0.24, 0.3	0.91, 0.93, 0.95, 0.97	0.8, 0.85, 0.9, 0.95	0.8, 0.9, 0.95, 0.99	Standard
14	0.9, 0.92, 0.95, 1.0	0.1, 0.2, 0.24, 0.3	0.91, 0.93, 0.95, 0.97	0.7, 0.75, 0.9, 0.95	0.75, 0.9, 0.95, 0.99	Standard
15	0.9, 0.92, 0.95, 1.0	0.1, 0.2, 0.24, 0.3	0.91, 0.93, 0.95, 0.97	0.6, 0.7, 0.8, 0.95	0.7, 0.85, 0.9, 0.99	Standard
16	0.9, 0.92, 0.95, 1.0	0.1, 0.3, 0.4, 0.5	0.91, 0.94, 0.96, 0.99	0.8, 0.85, 0.9, 0.95	0.8, 0.9, 0.95, 0.99	Standard
17	0.9, 0.92, 0.95, 1.0	0.1, 0.3, 0.4, 0.5	0.91, 0.94, 0.96, 0.99	0.7, 0.75, 0.9, 0.95	0.75, 0.9, 0.95, 0.99	Standard
18	0.9, 0.92, 0.95, 1.0	0.1, 0.3, 0.4, 0.5	0.91, 0.94, 0.96, 0.99	0.6, 0.7, 0.8, 0.95	0.7, 0.85, 0.9, 0.99	Standard
19	0.85, 0.87, 0.97, 1.0	0.1, 0.14, 0.15, 0.2	0.91, 0.92, 0.93, 0.94	0.8, 0.85, 0.9, 0.95	0.8, 0.9, 0.95, 0.99	Standard
20	0.85, 0.87, 0.97, 1.0	0.1, 0.14, 0.15, 0.2	0.91, 0.92, 0.93, 0.94	0.7, 0.75, 0.9, 0.95	0.75, 0.9, 0.95, 0.99	Standard
21	0.85, 0.87, 0.97, 1.0	0.1, 0.14, 0.15, 0.2	0.91, 0.92, 0.93, 0.94	0.6, 0.7, 0.8, 0.95	0.7, 0.85, 0.9, 0.99	Standard
22	0.85, 0.87, 0.97, 1.0	0.1, 0.2, 0.24, 0.3	0.91, 0.93, 0.95, 0.97	0.8, 0.85, 0.9, 0.95	0.8, 0.9, 0.95, 0.99	Standard
23	0.85, 0.87, 0.97, 1.0	0.1, 0.2, 0.24, 0.3	0.91, 0.93, 0.95, 0.97	0.7, 0.75, 0.9, 0.95	0.75, 0.9, 0.95, 0.99	Standard
24	0.85, 0.87, 0.97, 1.0	0.1, 0.2, 0.24, 0.3	0.91, 0.93, 0.95, 0.97	0.6, 0.7, 0.8, 0.95	0.7, 0.85, 0.9, 0.99	Standard
25	0.85, 0.87, 0.97, 1.0	0.1, 0.3, 0.4, 0.5	0.91, 0.94, 0.96, 0.99	0.8, 0.85, 0.9, 0.95	0.8, 0.9, 0.95, 0.99	Standard
26	0.85, 0.87, 0.97, 1.0	0.1, 0.3, 0.4, 0.5	0.91, 0.94, 0.96, 0.99	0.7, 0.75, 0.9, 0.95	0.75, 0.9, 0.95, 0.99	Standard
27	0.85, 0.87, 0.97, 1.0	0.1, 0.3, 0.4, 0.5	0.91, 0.94, 0.96, 0.99	0.6, 0.7, 0.8, 0.95	0.7, 0.85, 0.9, 0.99	Standard

* Trapezoidal distribution (minimum value, mode 1 value, mode 2 value, maximum value).
W_1: Selection probability
W_2: Sensitivity of cause of death classification for abortion related PAC
W_3: Specificity of cause of death classification for abortion related PAC
W_4: Sensitivity of cause of death classification
W_5: Specificity of cause of death classification
RE: Random Error

Table 3 Results from traditional bivariable and multivariable logistic regression of age on unsafe abortion

Exposure of interest	Unadjusted OR	95%CI	p-value	Adjusted OR*	95% CI	p-value
Age (Continuous)	0.70	0.53, 0.92	0.01	0.69	0.53, 0.92	0.01
Age						
<20 years of age	25.0	2.9, 216.1	0.003	26.4	3.0, 231.7	0.003
>20 years of age (reference)	-----	----	---	---	-----	---

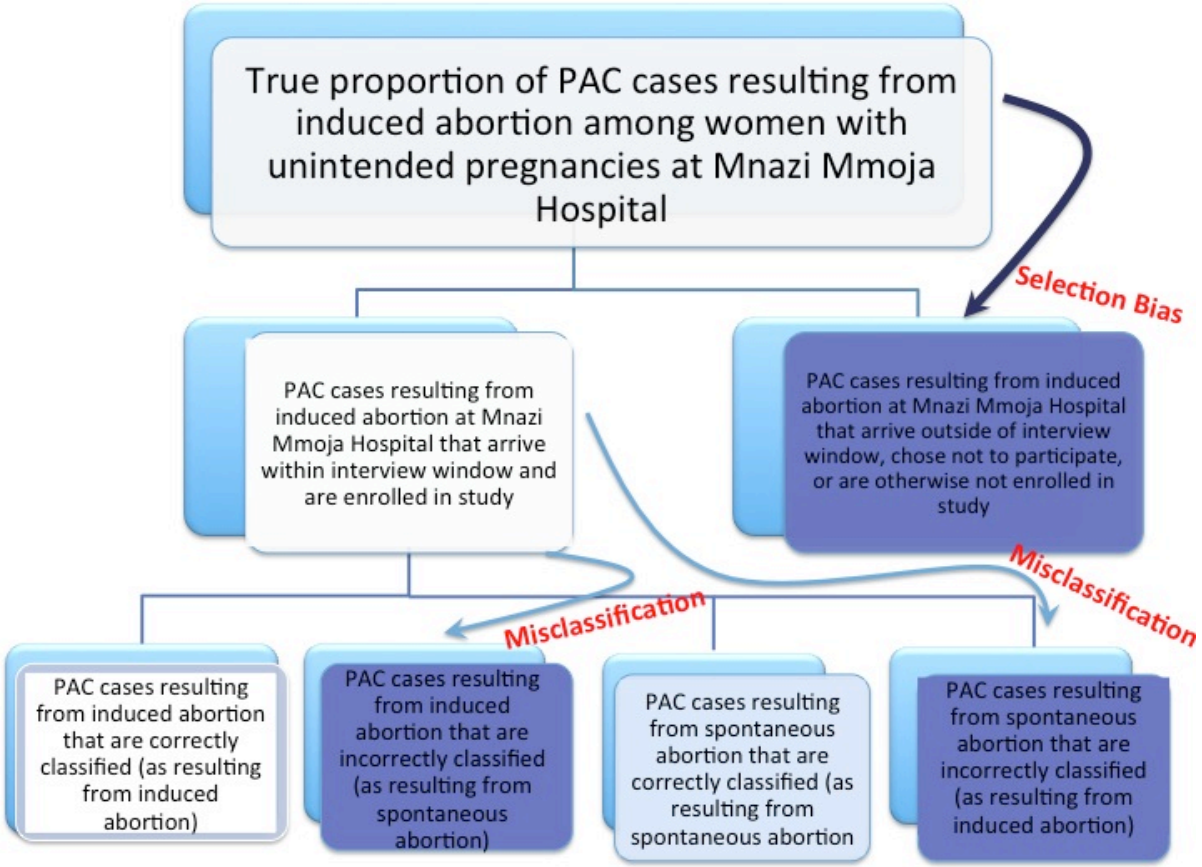
*Adjusted for years of education (continuous), and empowerment (categorical)

Table 4 Results from multiple bias analysis of unadjusted logistic regression of age (dichotomous) on unsafe abortion corrected for selection bias and misclassification

Model	Bias Parameter	Median Odds Ratio	2.5 Percentile	97.5 Percentile
1	Selection Bias (Narrow), Misclassification ARPAC* (Narrow), Misclassification NRPAC§ (Narrow)	47.51	3.07	1534.87
2	Selection Bias (Narrow), Misclassification ARPAC (Narrow), Misclassification NRPAC (Medium)	37.88	2.28	1280.31
3	Selection Bias (Narrow), Misclassification ARPAC (Narrow), Misclassification NRPAC (Wide)	24.77	1.60	782.31
4	Selection Bias (Narrow), Misclassification ARPAC (Medium), Misclassification NRPAC (Narrow)	70.48	3.70	3211.41
5	Selection Bias (Narrow), Misclassification ARPAC (Medium), Misclassification NRPAC (Medium)	36.05	1.94	1679.90
6	Selection Bias (Narrow), Misclassification ARPAC (Medium), Misclassification NRPAC (Wide)	81.28	3.96	3868.19
7	Selection Bias (Narrow), Misclassification ARPAC (Wide), Misclassification NRPAC (Narrow)	62.22	2.99	3523.67
8	Selection Bias (Narrow), Misclassification ARPAC (Wide), Misclassification NRPAC (Medium)	37.17	2.00	1820.64
9	Selection Bias (Narrow), Misclassification ARPAC (Wide), Misclassification NRPAC (Wide)	47.07	3.08	1550.14
10	Selection Bias (Medium), Misclassification ARPAC (Narrow), Misclassification NRPAC (Narrow)	37.87	2.32	1298.56
11	Selection Bias (Medium), Misclassification ARPAC (Narrow), Misclassification NRPAC (Medium)	24.69	1.58	781.00
12	Selection Bias (Medium), Misclassification ARPAC (Narrow), Misclassification NRPAC (Wide)	69.49	3.89	3250.30
13	Selection Bias (Medium), Misclassification ARPAC (Medium), Misclassification NRPAC (Narrow)	55.03	3.08	2908.93
14	Selection Bias (Medium), Misclassification ARPAC (Medium), Misclassification NRPAC (Medium)	34.89	1.94	1577.69
15	Selection Bias (Medium), Misclassification ARPAC (Medium), Misclassification NRPAC (Wide)	78.49	4.14	3692.79
16	Selection Bias (Medium), Misclassification ARPAC (Wide), Misclassification NRPAC (Narrow)	57.52	3.09	3121.79
17	Selection Bias (Medium), Misclassification ARPAC (Wide), Misclassification NRPAC (Medium)	38.22	2.19	1785.57
18	Selection Bias (Medium), Misclassification ARPAC (Wide), Misclassification NRPAC (Wide)	46.94	3.04	1453.51
19	Selection Bias (Wide), Misclassification ARPAC (Narrow), Misclassification NRPAC (Narrow)	37.99	2.04	1763.08
20	Selection Bias (Wide), Misclassification ARPAC (Narrow), Misclassification NRPAC (Medium)	24.73	1.58	805.91
21	Selection Bias (Wide), Misclassification ARPAC (Narrow), Misclassification NRPAC (Wide)	70.65	3.88	3277.90
22	Selection Bias (Wide), Misclassification ARPAC (Medium), Misclassification NRPAC (Narrow)	54.48	2.79	2997.12
23	Selection Bias (Wide), Misclassification ARPAC (Medium), Misclassification NRPAC (Medium)	34.94	2.07	1539.23
24	Selection Bias (Wide), Misclassification ARPAC (Medium), Misclassification NRPAC (Wide)	75.91	4.26	4089.34
25	Selection Bias (Wide), Misclassification ARPAC (Wide), Misclassification NRPAC (Narrow)	32.98	1.97	1103.82
26	Selection Bias (Wide), Misclassification ARPAC (Wide), Misclassification NRPAC (Medium)	61.30	3.46	2944.10
27	Selection Bias (Wide), Misclassification ARPAC (Wide), Misclassification NRPAC (Wide)	37.95	2.18	1743.43

*Induced Abortion Related Post Abortion Care §Miscarriage Related Post Abortion Care

Figure 1: Bias Framework: understanding systematic error present in study of PAC cases among women with unwanted pregnancies at Mnazi Mmoja Hospital



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Conclusion

As the results of the preceding analyses suggest, it is likely that unsafe abortion has been significantly underestimated as a cause of maternal death and post abortion care. These results have clear implications for increasing efforts aimed at the proven interventions which help to decrease abortion related mortality and morbidity: reducing unintended pregnancy, ensuring access to safe abortion services where it is legal, increasing access to safe abortion services where laws have the potential to be revised, and providing access to comprehensive post abortion care with contraceptive counseling in places where access to abortion remains highly restricted. These results also have implications for scientists committed to producing sound evidence in a field with endemic measurement challenges. Improving methods to quantify the direction and magnitude of systematic error in studies, and integrate such information into the interpretation of results concerning the burden of unsafe abortion-related mortality and the proportion of post abortion care due to post abortion care is the necessary first step in understanding these grave public health concerns, and targeting interventions that appropriately address their underlying causes.

Appendices

Appendix 1: Systematic Review Search Strategy

Pubmed:

1. Limit to human
2. (maternal adj4 mortal$).af.
3. (maternal adj4 death$).af.
4. (pregnan$ adj4 death$).af.
5. (pregnan$ adj4 mortalit$).af.
6. exp abortion
7. exp pregnancy termination
8. exp menstrual regulation
9. exp verbal autopsy
10. or/2-9
11. 2-4 and 6
12. 2-4 and 7
13. 2-4 and 8
14. 2-8 and 9
15. "2000".yr. and 2-9
16. "2001".yr. and 2-9
17. "2002".yr. and 2-9
18. "2003".yr. and 2-9
19. "2004".yr. and 2-9
20. "2005".yr. and 2-9
21. “2006”,yr. and 2-9
22. “2007”,yr. and 2-9
23. “2008”,yr. and 2-9
24. “2009”,yr. and 2-9
25. “2010”,yr. and 2-9
26. “2011”,yr. and 2-9

Medline (Ovid):

1. Limit to human
2. (maternal adj4 mortal$).af.
3. (maternal adj4 death$).af.
4. (pregnan$ adj4 death$).af.
5. (pregnan$ adj4 mortalit$).af.
6. exp abortion
7. exp pregnancy termination
8. exp menstrual regulation
9. exp verbal autopsy
10. or/2-9
11. 2-4 and 6
12. 2-4 and 7
13. 2-4 and 8

14. 2-8 and 9
15. "2000".yr. and 2-9
16. "2001".yr. and 2-9
17. "2002".yr. and 2-9
18. "2003".yr. and 2-9
19. "2004".yr. and 2-9
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22. “2007”,yr. and 2-9
23. “2008”,yr. and 2-9
24. “2009”,yr. and 2-9
25. “2010”,yr. and 2-9
26. “2011”,yr. and 2-9

EMBASE (Ovid):

1. Limit to human
2. (maternal adj4 mortal$).af.
3. (maternal adj4 death$).af.
4. (pregnan$ adj4 death$).af.
5. (pregnan$ adj4 mortalit$).af.
6. exp abortion
7. exp pregnancy termination
8. exp menstrual regulation
9. exp verbal autopsy
10. or/2-9
11. 2-4 and 6
12. 2-4 and 7
13. 2-4 and 8
14. 2-8 and 9
15. "2000".yr. and 2-9
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22. “2007”,yr. and 2-9
23. “2008”,yr. and 2-9
24. “2009”,yr. and 2-9
25. “2010”,yr. and 2-9
26. “2011”,yr. and 2-9

POPLINE

Under keywords:

="Maternal Mortality" / =”Maternal Death” /="Pregnancy Death" / ="Pregnancy Mortality" / ="Abortion Induced" / = “Abortion”/ = “Menstrual Regulation” /= “Verbal Autopsy”

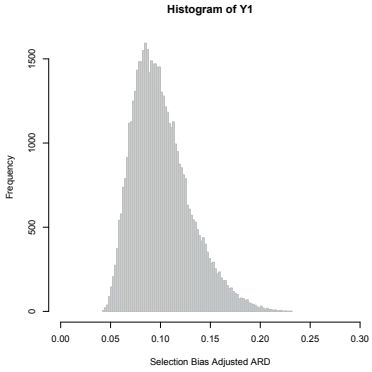
JSTOR

Under Keywords:
="Maternal Mortality" / =”Maternal Death” /="Pregnancy Death" / ="Pregnancy Mortality" / ="Abortion Induced" / = “Abortion”/ = “Menstrual Regulation” /= “Verbal Autopsy”

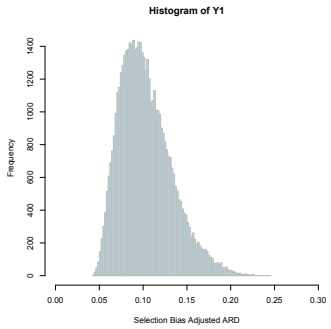
Appendix 2: Figures for multiple bias analysis of proportion abortion-related deaths

Study A: Mariaga

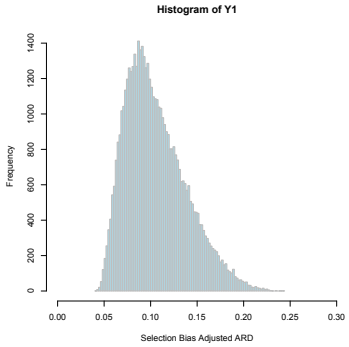
Proportion of abortion related deaths adjusted for selection bias under Narrow, Medium and Wide probability distributions



Narrow

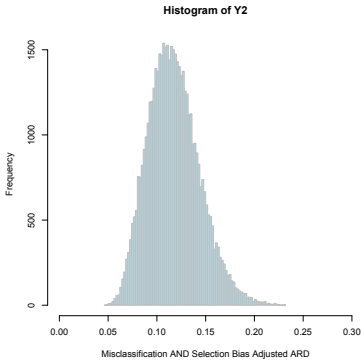


Medium

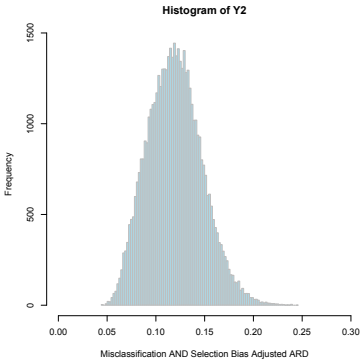


Wide

Proportion of abortion related deaths adjusted for selection bias and misclassification under Narrow, Medium and Wide probability distributions



Narrow, Narrow



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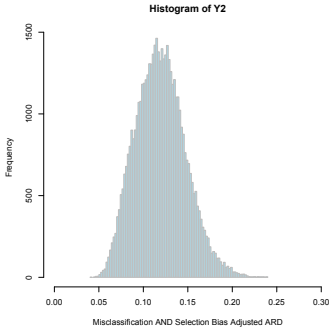
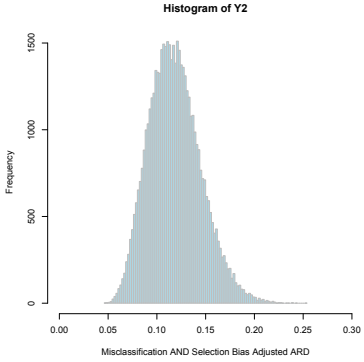


Narrow, Wide



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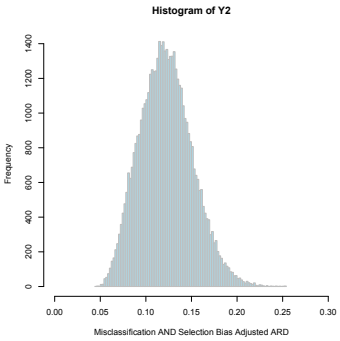

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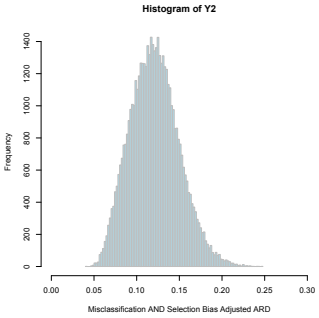

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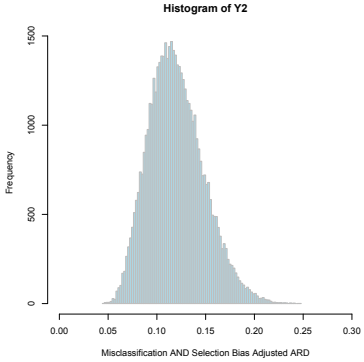
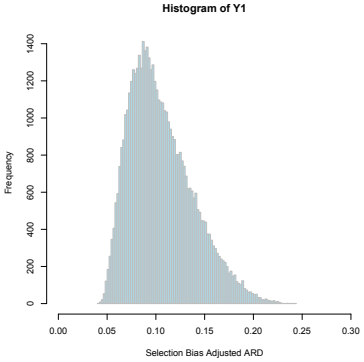
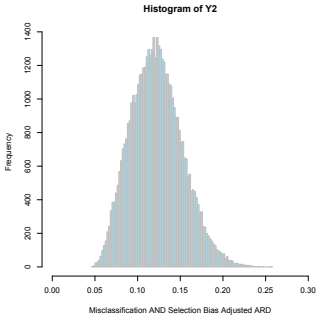


Wide, Narrow

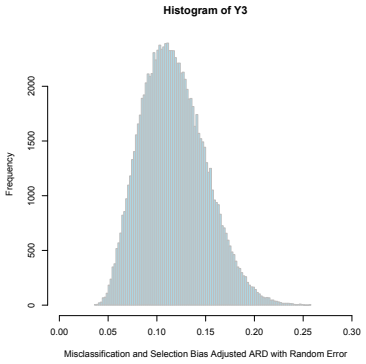


Wide, Medium

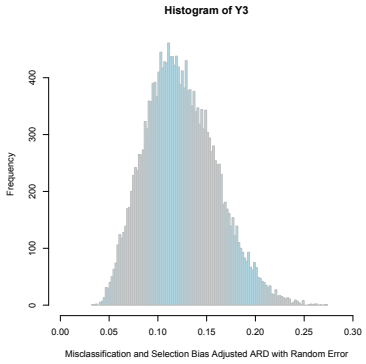


Wide, Wide

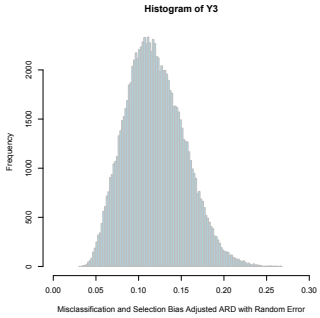
Proportion of abortion related deaths adjusted for selection bias, misclassification, and random error under Narrow, Medium and Wide probability distributions



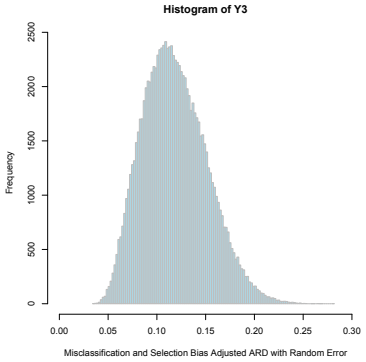
Narrow, Narrow



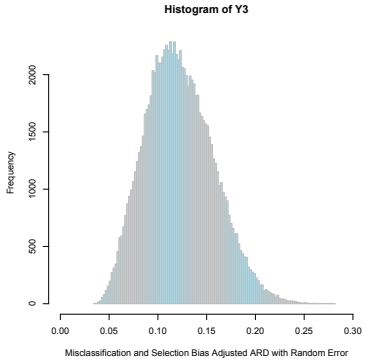
Narrow, Medium



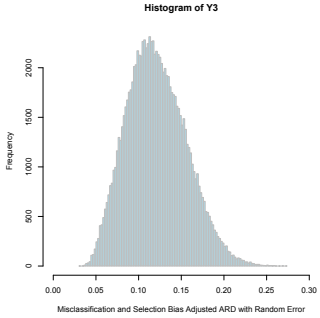
Narrow, Wide



Medium, Narrow



Medium, Medium



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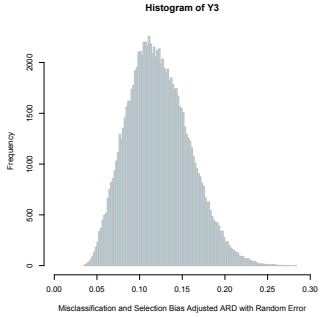
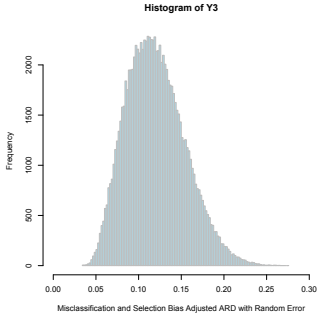
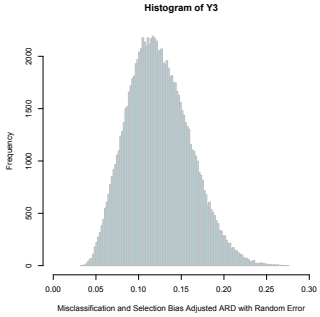


Wide, Narrow



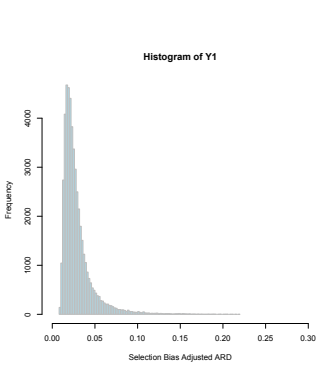
Wide, Medium



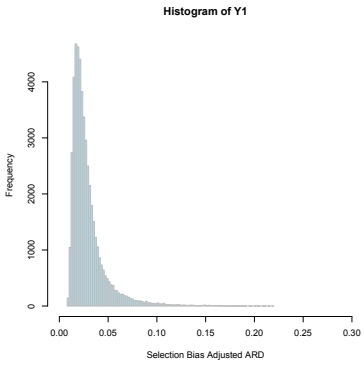
Wide, Wide

Study B: Jafarey

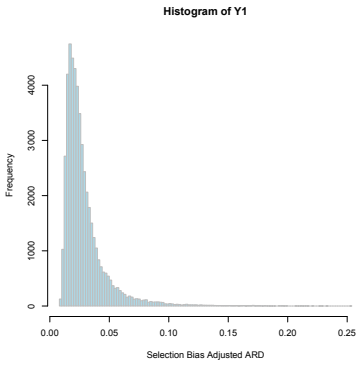
Proportion of abortion related deaths adjusted for selection bias under Narrow, Medium and Wide probability distributions



Narrow

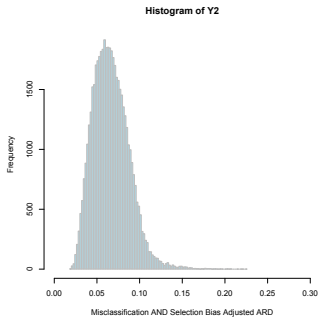


Medium

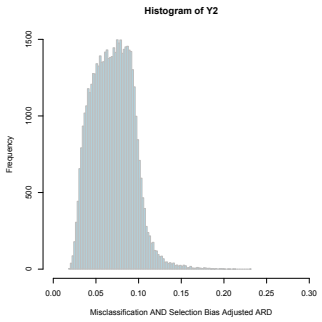


Wide

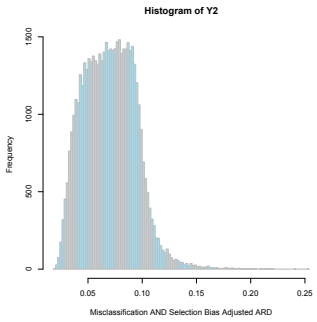
Proportion of abortion related deaths adjusted for selection bias and misclassification under Narrow, Medium and Wide probability distributions



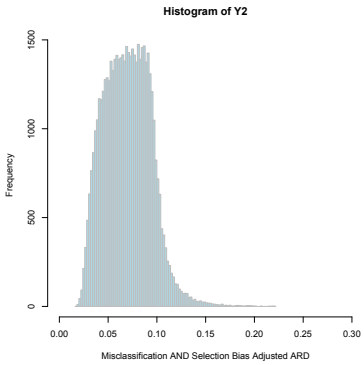
Narrow, Narrow



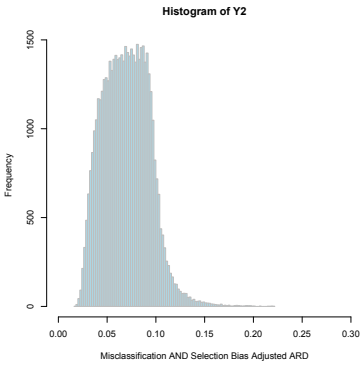
Narrow, Medium



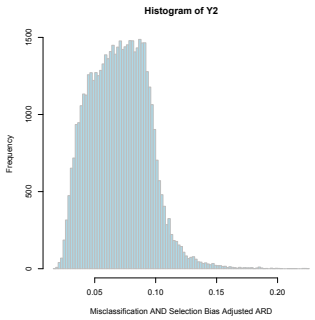
Narrow, Wide



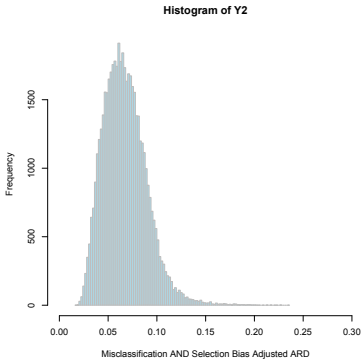
Medium, Narrow



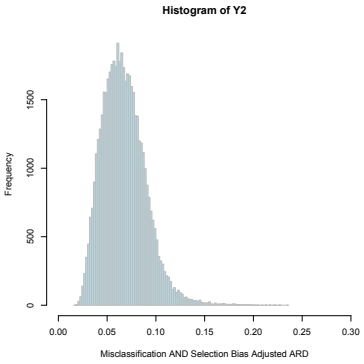
Medium, Medium



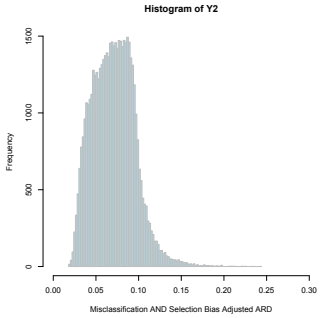
Medium, Wide



Wide, Narrow

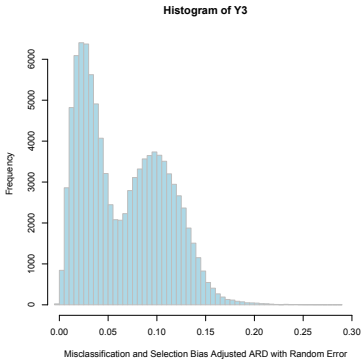


Wide, Medium

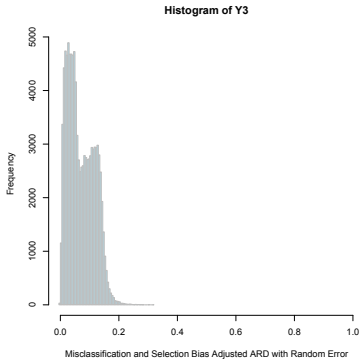


Wide, Wide

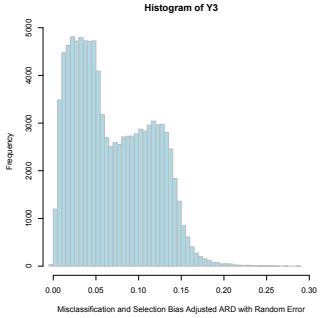
Proportion of abortion related deaths adjusted for selection bias, misclassification, and random error under Narrow, Medium and Wide probability distributions



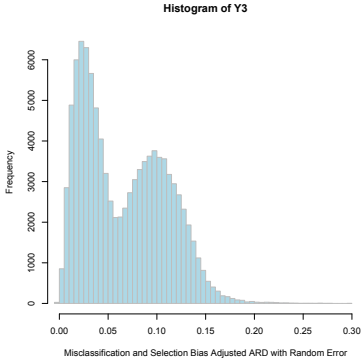
Narrow, Narrow



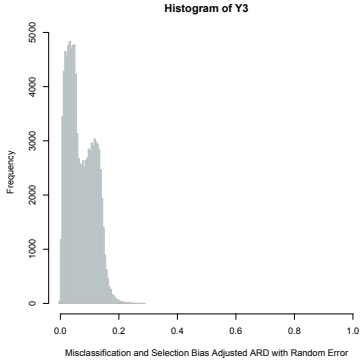
Narrow, Medium



Narrow, Wide



Medium, Narrow



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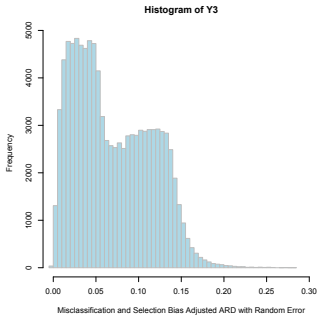
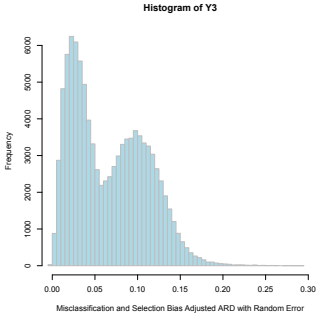
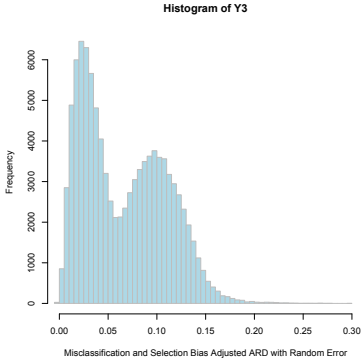


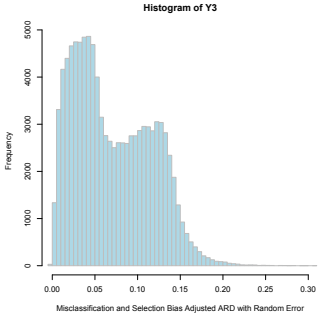
Medium, Wide



Wide, Narrow



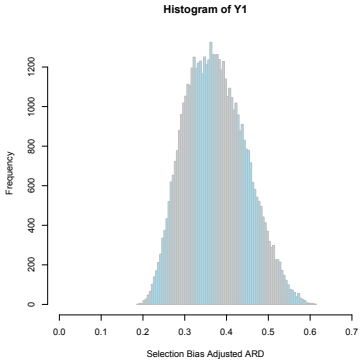
Wide, Medium



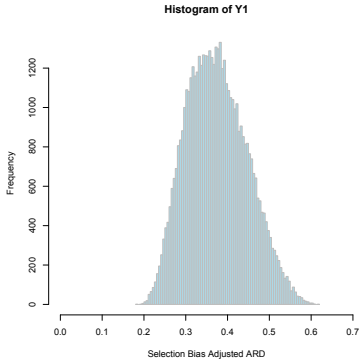
Wide, Wide

Study C: Oyieke

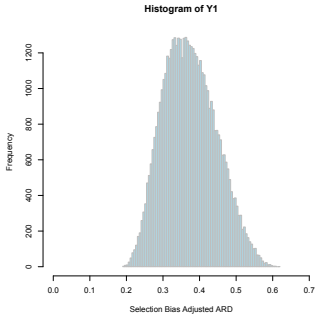
Proportion of abortion related deaths adjusted for selection bias under Narrow, Medium and Wide probability distributions



Narrow

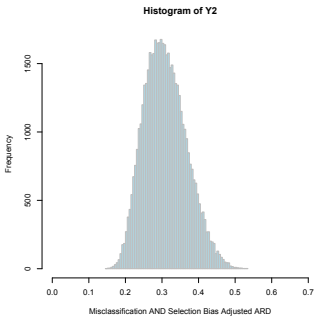


Medium

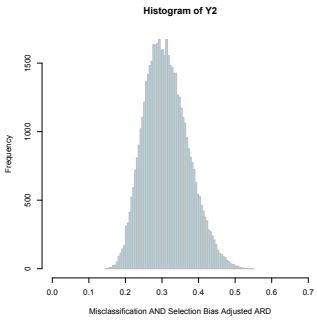


Wide

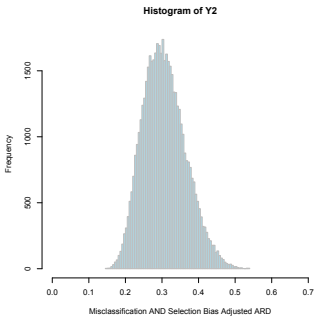
Proportion of abortion related deaths adjusted for selection bias and misclassification under Narrow, Medium and Wide probability distributions



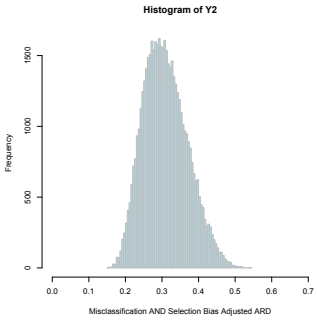
Narrow, Narrow



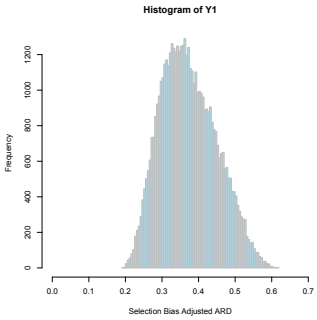
Narrow, Medium



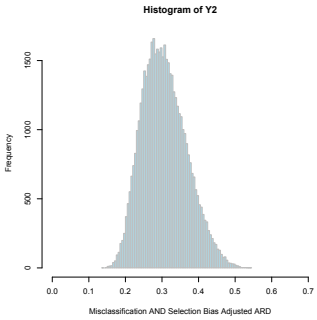
Narrow, Wide



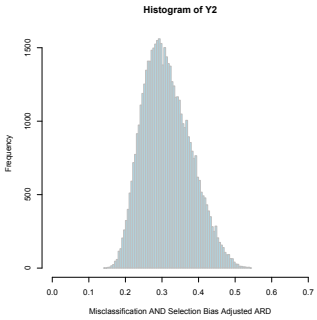
Medium, Narrow



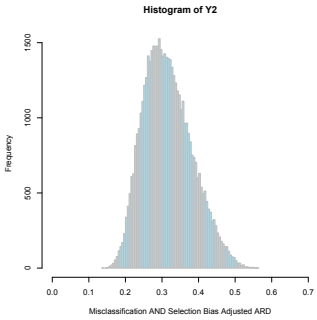
Medium, Medium



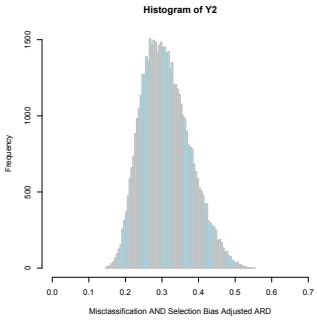
Medium, Wide



Wide, Narrow

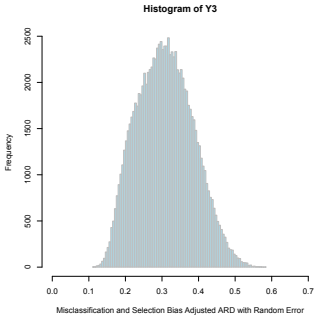


Wide, Medium

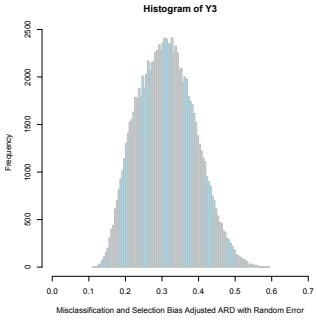


Wide, Wide

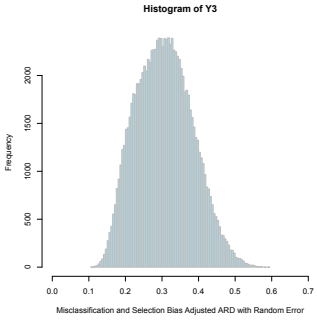
Proportion of abortion related deaths adjusted for selection bias, misclassification, and random error under Narrow, Medium and Wide probability distributions



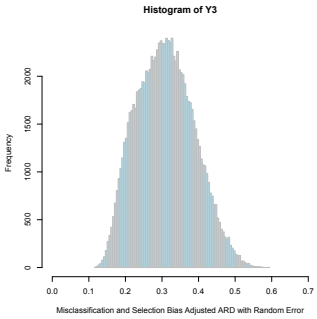
Narrow, Narrow



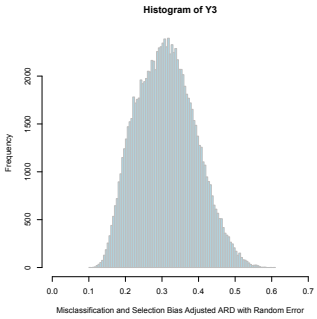
Narrow, Medium



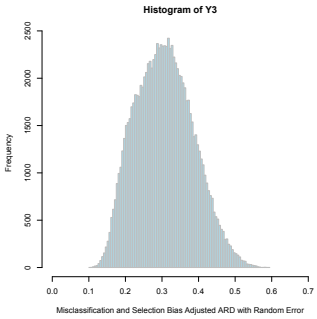
Narrow, Wide



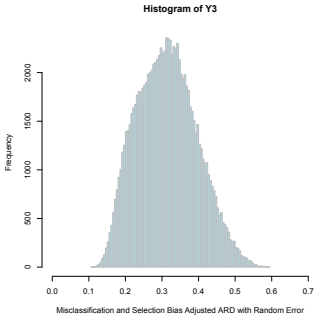
Medium, Narrow



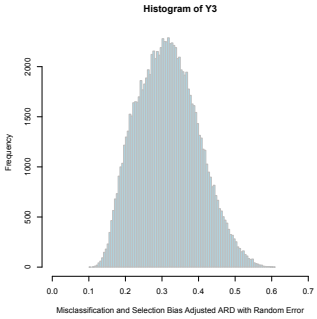
Medium, Medium



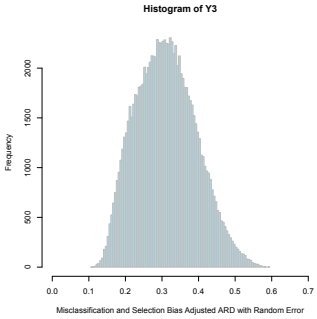
Medium, Wide



Wide, Narrow



Wide, Medium



Wide, Wide