RESEARCH

Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration

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EDITORIAL by Geddes and colleagues

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ABSTRACT

Objective To examine the risk of suicidal behaviour within clinical trials of antidepressants in adults.

Design Meta-analysis of 372 double blind randomised placebo controlled trials.

Setting Drug development programmes for any indication in adults.

Participants 99 231 adults assigned to antidepressants or placebo. Median age was 42 and 63.1% were women. Indications for treatment were major depression (45.6%), other depression (4.6%), other psychiatric disorders (27.6%), and non-psychiatric disorders (22.2%).

Main outcome measures Suicidal behaviour (completed suicide, attempted suicide, or preparatory acts) and ideation.

Results For participants with non-psychiatric indications, suicidal behaviour and ideation were extremely rare. For those with psychiatric indications, risk was associated with age. For suicidal behaviour or ideation and for suicidal behaviour only, the respective odds ratios were 1.62 (95% confidence interval 0.97 to 2.71) and 2.30 (1.04 to 5.09) for participants aged <25, 0.79 (0.64 to 0.98) and 0.87 (0.58 to 1.29) for those aged 25-64, and 0.37 (0.18 to 0.76) and 0.06 (0.01 to 0.58) for those aged ≥65. When age was modelled as a continuous variable, the odds ratio for suicidal behaviour or ideation declined at a rate of 2.6% per year of age (−3.9% to −1.3%, P=0.0001) and the odds ratio for suicidal behaviour declined at a rate of 4.6% per year of age (−7.4% to −1.8%, P=0.001).

Conclusions Risk of suicidality associated with use of antidepressants is strongly age dependent. Compared with placebo, the increased risk for suicidality and suicidal behaviour among adults under 25 approaches that seen in children and adolescents. The net effect seems to be neutral on suicidal behaviour but possibly protective for suicidal ideation in adults aged 25-64 and to reduce the risk of both suicidality and suicidal behaviour in those aged ≥65.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Clinical trials of antidepressants in children and adolescents have shown an increased risk of suicidal thoughts or behaviour relative to those who received placebo

Epidemiological studies have tended to show an association of lower rates of suicide with higher rates of antidepressant use

WHAT THIS STUDY ADDS

Effects on suicidal thoughts or behaviour associated with antidepressants observed in clinical trials are strongly age dependent; risk declines and benefit increases with increasing age

The age related gradient seems steeper for suicidal behaviour than for ideation alone

Beneficial effects on suicidal thoughts and ideation were most strongly associated with older people treated for major depression, whereas harmful effects were most strongly associated with younger people treated for psychiatric disorders other than depression

INTRODUCTION

There is a longstanding belief that antidepressants might have an early "activating effect" that gives depressed patients the energy to follow through on suicidal impulses before the mood improvement takes effect. Concern about an increased risk of suicide with fluoxetine led to a meeting of the US Food and Drug Administration (FDA) psychopharmacologic drugs advisory committee in 1991. The committee concluded that there was no clear evidence of an increased risk.

Over the next decade, additional data were accumulated as applications for newer antidepressants were reviewed. Three subsequent analyses of adult data from FDA reviews, and the medicines evaluation board of the Netherlands, concluded that the risk of completed suicide was the same for drugs and placebo.[1 2 3]

Analysis of data from several paediatric trials on paroxetine in 2003 raised a concern that antidepressant drug treatment might have led to attempted suicide and ideation in children and adolescents. A report presented to the FDA in 2004, based on manufacturers' data from trials in children and adolescents, showed a relative risk for suicidal behaviour or ideation of 1.95 (95% confidence interval 1.28 to 2.98) for those treated with antidepressants compared with those given placebo.[4] The committees recommended that the FDA add a boxed warning to antidepressant labelling and review clinical trials of antidepressants in adults. Two previous published meta-analyses in adults did not have access to

primary data, and could not validate the identification and classification of suicidal events.[5 6] We carried out a review to respond to the committees' request.

METHODS

Data collection

The FDA asked eight industry sponsors of 12 antidepressant products for datasets from all double blind randomised placebo controlled trials of antidepressant in adults for any indication.

Datasets were received by the FDA between September 2005 and September 2006. Sponsors provided information on the dose, duration, number of participants per trial, and exclusion criteria. Sponsors were asked to search their databases for adverse events reported during the double blind phase of treatment for terms related to suicidality. The datasets included 406 clinical trials with 103 491 participants. Six trials were duplicated. We excluded 28 other trials and 608 participants, leaving a total of 372 trials with 99 231 participants.

Determination of suicidality outcomes

Sponsors adjudicated events possibly related to suicidality from case narratives. Adjudicators were blinded to treatment assignment and classified events into seven mutually exclusive categories: 1 completed suicide, 2 suicide attempt, 3 preparatory acts toward imminent suicidal behaviour, 4 suicidal ideation, 5 self injurious behaviour, intent unknown, 6 not enough information (fatal), and 7 not enough information (non-fatal).[7]

Three trained individuals independently rated events.

Statistical analysis

The primary outcome was defined as suicidal ideation or worse (categories 1, 2, 3, or 4). The second outcome variable was preparatory actions or worse (categories 1, 2, or 3), also called suicidal behaviour. We used conditional logistic regression to calculate odds ratios and obtained risk differences with population averaged general estimating equations. To examine trial heterogeneity, we added treatment by trial interaction terms to the model. Heterogeneity of effect by drug and drug class were similarly modelled. We modelled age and age-treatment interaction as continuous variables. Subgroup analyses were performed based on demographics, characteristics at the trial level, indication, and drug class.

RESULTS

Characteristics of the data

The total duration of observation was 15 505 person years. There were eight reported completed suicides, 134 reported suicide attempts, 10 reports of preparations without attempted suicide, and 378 reported suicidal ideation alone. Incidence rates for other depressive disorders and psychiatric disorders other than depression were about two thirds of that for major depression. The rates for non-psychiatric disorders were much lower than for psychiatric disorders and consisted almost entirely of suicidal ideation alone (see bmj.com).

Estimates of risk of suicidality associated with antidepressant treatment

Table 1 shows the estimated odds ratios and risk differences for suicidal ideation or worse associated with assignment to antidepressant drug treatment compared with placebo. For the entire dataset, the odds ratio was 0.85 (95% confidence interval 0.71 to 1.02). The estimated odds ratio for preparatory acts or worse was 1.12 (0.79 to 1.58). The odds ratio for completed suicide (2.13) was higher for those treated with an antidepressant, but this was based on just eight events and was not significant (0.41 to 10.99).

Table 1 also compares risk of suicidality by indication. The psychiatric indication categories seem remarkably similar, while the non-psychiatric categories seem similar to each other but distinct from the psychiatric categories. The difference between the psychiatric diagnoses and the non-psychiatric diagnoses, however, was not significant (P=0.25). As there were few events in the non-psychiatric categories we have limited further analyses to the 77 207 participants in 295 clinical trials for psychiatric indications.

We examined odds ratios and risk differences for suicidality for antidepressant treatment in psychiatric disorders by drug and drug class. For the entire population

Table 1 | Suicidality risk for active drug relative to placebo (ideation or worse) in all adults by indication

Indication category	Drug		Placebo		Odds ratio (95% CI), P value	Risk difference/1000 (95% CI), P value
	Events	Participants	Events	Participants		
All indications	326	63 327	204	35 904	0.85 (0.71 to 1.02), 0.08	−0.87 (−1.89 to 0.15), 0.10
Psychiatric indications:						
All	314	50 043	197	27 164	0.83 (0.69 to 1.00), 0.05	−1.28 (−2.57 to 0.00), 0.05
Major depression	218	30 485	123	14 728	0.85 (0.67 to 1.07), 0.16	−1.42 (−3.23 to 0.40), 0.12
Other depression	13	2744	9	1863	0.90 (0.38 to 2.14), 0.81	−0.15 (−4.40 to 4.11), 0.95
Other	83	16 814	65	10 573	0.79 (0.56 to 1.11), 0.17	−1.37 (−3.33 to 0.59), 0.17
Non-psychiatric indications	12	13 284	7	8740	1.47 (0.57 to 3.79), 0.42	0.28 (−0.50 to 1.05), 0.48
Behavioural indications	6	8144	3	5218	1.43 (0.35 to 5.86), 0.62	0.16 (−0.72 to 1.03), 0.72
Other indications	6	5140	4	3522	1.51 (0.42 to 5.40), 0.53	0.38 (−0.96 to 1.73), 0.58

Table 2 | Suicidality risk by age for active drug relative to placebo in adults with psychiatric disorders

Age range	Drug		Placebo		Odds ratio (95% CI), P value	Risk difference/1000 (95% CI), P value
	Events	Participants	Events	Participants		
Ideation or worse						
<25	64	4780	21	2621	1.62 (0.97 to 2.71), 0.07	5.34 (0.61 to 10.1), 0.03
≥25	250	45 263	176	24 543	0.74 (0.60 to 0.90), 0.003	−1.96 (−3.28 to −0.64), 0.004
25-64	238	41 331	152	22 126	0.79 (0.64 to 0.98), 0.03	−1.48 (−2.84 to −0.11), 0.03
25-34	85	12 479	54	6813	0.76 (0.53 to 1.08), 0.13	−1.61 (−4.23 to 1.02), 0.23
35-44	74	14 002	48	7564	0.78 (0.53 to 1.14), 0.2	−1.33 (−3.52 to 0.86), 0.24
45-54	60	9805	34	5074	0.94 (0.60 to 1.46), 0.78	−0.64 (−3.43 to 2.15), 0.65
55-64	19	5045	16	2675	0.62 (0.30 to 1.27), 0.19	−1.94 (−5.18 to 1.30), 0.24
≥65	12	3907	24	2397	0.37 (0.18 to 0.76), 0.007	−6.34 (−10.8 to −1.91), 0.005
65-74	9	2663	12	1595	0.53 (0.22 to 1.33), 0.18	−3.87 (−8.69 to 0.95), 0.12
≥75	3	1244	12	790	0.22 (0.06 to 0.79), 0.02	−12.4 (−21.7 to −3.16), 0.01
Ideation alone						
<25	32	4780	13	2621	1.19 (0.61 to 2.35), 0.61	1.71 (−1.84 to 5.26), 0.34
≥25	180	45 263	135	24 543	0.70 (0.55 to 0.88), 0.003	−1.73 (−2.86 to −0.59), 0.003
25-64	169	41 331	118	22 126	0.72 (0.56 to 0.92), 0.01	−1.53 (−2.71 to −0.35), 0.01
25-34	58	12 479	37	6813	0.73 (0.48 to 1.13), 0.16	−1.16 (−3.31 to 0.99), 0.29
35-44	53	14 002	37	7564	0.74 (0.47 to 1.16), 0.19	−1.31 (−3.20 to 0.59), 0.18
45-54	44	9805	30	5074	0.77 (0.47 to 1.25), 0.29	−1.5 (−4.05 to 1.05), 0.25
55-64	14	5045	14	2675	0.56 (0.25 to 1.27), 0.16	−2.01 (−4.90 to 0.87), 0.17
≥65	11	3907	17	2397	0.53 (0.25 to 1.16), 0.11	−3.32 (−6.86 to 0.22), 0.07
65-74	8	2663	8	1595	0.83 (0.30 to 2.28), 0.72	−1.49 (−5.36 to 2.39), 0.45
≥75	3	1244	9	790	0.29 (0.08 to 1.11), 0.07	−8.54 (−16.6 to −0.53), 0.04
Suicidal behaviour						
<25	32	4780	8	2621	2.30 (1.04 to 5.09), 0.04	3.64 (0.51 to 6.77), 0.02
≥25	70	45 263	41	24 543	0.87 (0.58 to 1.29), 0.48	−0.19 (−0.84 to 0.46), 0.57
25-64	69	41 331	34	22 126	1.03 (0.68 to 1.58), 0.88	0.09 (−0.58 to 0.76), 0.8
25-34	27	12 479	17	6813	0.81 (0.43 to 1.52), 0.53	−0.36 (−1.82 to 1.10), 0.63
35-44	21	14 002	11	7564	0.89 (0.42 to 1.87), 0.75	−0.00 (−1.10 to 1.10), 1.00
45-54	16	9805	4	5074	2.29 (0.73 to 7.14), 0.15	0.84 (−0.27 to 1.96), 0.14
55-64	5	5045	2	2675	0.89 (0.17 to 4.73), 0.89	0.20 (−1.25 to 1.66), 0.78
≥65	1	3907	7	2397	0.06 (0.01 to 0.58), 0.01	−2.85 (−5.23 to −0.48), 0.02
65-74	1	2663	4	1595	0.09 (0.01 to 0.95), 0.04	−2.18 (−4.80 to 0.43), 0.10
≥75	0	1244	3	790	0 (0 to ∞), 1.00	−3.71 (−7.04 to −0.37), 0.03

with psychiatric disorders, there was a decrease in suicidality with treatment. Statistical tests for differences in effect among drugs and drug classes had negative results, with the exception of some indication of differences among SSRIs. The odds ratios for suicidal behaviour were slightly higher than those observed for suicidality.

Estimates of heterogeneity in treatment effect among trials and of interaction of treatment effect with status of a drug as test drug or active control, trial location, sex, and ethnicity were all non-significant (P>0.35).

Table 2 shows the risks by age for suicidality associated with assignment to antidepressant treatment for adults with psychiatric disorders. The most striking observation is the higher odds ratio and risk difference with antidepressant treatment than with placebo in those aged under 25 but lower odds ratio and risk difference in those aged 25 or older. There might also be a further distinction between a modest protective effect of antidepressants in people aged 25-64 and a stronger protective effect in those aged 65 and older. When we modelled age as a continuous variable, the odds ratio declined at a rate of 2.6% per year of age (−3.9% to −1.3%, P=0.001).

Table 2 also shows risks by age for suicidal ideation and suicidal behaviour. The decline in odds ratio and risk difference with age for suicidal ideation alone was relatively slight; the differences between major age categories were not significant, except when we modelled age as a continuous variable (change in odds ratio −1.8% per year of age, −3.3% to −0.4%, P=0.014). For suicidal behaviour, with a smaller number of events, the decline in odds ratios with age seems steeper and the differences between age categories were more significant. When we modelled age as a continuous variable, the odds ratio declined at a rate of 4.6% per year of age (−7.4% to −1.8%, P=0.001).

DISCUSSION

In contrast with the results of the review of paediatric studies on suicide and antidepressants by the US Food and Drug Administration (FDA),[4] pooled estimates for the adult population did not show an increased risk of suicidality. When we analysed results by age, however, we found an increased risk among adults aged under 25 that approached the risk seen in children and adolescents. The net effect seems moderately protective for adults aged 25-64 and more strongly protective in those aged 65 and older. This age related gradient seemed steeper for suicidal behaviour than for ideation alone.

The overall result is probably a consequence of the age distribution of the participants in the study population. This population was not chosen to be representative of the age distribution of antidepressant users.

If the population had skewed younger, the overall result would probably have shown a higher risk; if the population had skewed older, the overall risk would probably have been lower. The overall estimates are therefore not generalisable.

Strengths and limitations of this study

Our study analysed primary data from adverse event reports on individual subjects within a collection of clinical trials. The FDA has a record of virtually every company supported clinical trial performed on people in the US as well as reports of the results of those studies. In many cases the study reports included the original datasets and adverse event reports.

The main limitation of our study is its inability to address all the patients and circumstances with an indication for antidepressants. Patients at highest risk for suicide are extremely unlikely to be entered into placebo controlled trials. Moreover, most of the studies included in this analysis involved the initial treatment of an acute condition over eight to 10 weeks of observation. Patients receiving antidepressants for maintenance of a chronic condition or prevention of relapse might not be affected in the same way as acutely treated patients. This study can not resolve whether antidepressants affect the risk of death by suicide; even in a population of tens of thousands, there were only a handful of cases.

Results of other studies

Several case-control studies have addressed the question of a differential risk of antidepressant induced suicidality across the age spectrum. Olfson et al and Martinez et al found evidence of an increased risk of suicidality in patients aged 18 and younger treated with antidepressants.[8 9] The case-control methods used in these studies is subject to confounding—notably, differential prescribing to patients perceived to be sicker and at greater risk of suicidal behaviour.

Apart from the finding of age related risk, the results are consistent with published meta-analyses of clinical trials of SSRIs in adults conducted by Gunnell et al[5] and Fergusson et al.[6]

Population based studies have compared patterns of antidepressant prescribing and suicide rates.[10] Studies in Finland, Sweden, Hungary, Australia, one study in Britain, and a Europe-wide study showed an inverse correlation between antidepressant use and suicide rates, but studies in Italy, Iceland, and Denmark did not show a relation. A study from Northern Ireland showed an inverse correlation in adults over age 30 but found no relation between antidepressant use and suicide in adults aged 20-30.[11] In the US, Gibbons et al found the prescribing of SSRIs and other newer antidepressants was associated with lower suicide rates and tricyclic prescribing was associated with increased suicide rates.[12] The ecological approach taken by these studies, however, does not allow causal conclusions.

Explanations and implications

Some have argued that an observed increase in suicidality with drug treatment could be the result of ascertainment bias: an increase in reporting of suicidality rather than a true increase. Our findings argue against this explanation. Ascertainment bias cannot explain the observed age relatedness of the findings.

If suicide is a response to the symptoms of depression, treatments proved to reduce these symptoms ought to reduce the risk of suicide. Our study suggests, however, that the relation between suicidality, age, and antidepressant treatment is generalisable beyond those with major depressive disorder to everyone with psychiatric diagnoses. These findings support the idea that antidepressant drugs can have two separate effects: an undesirable effect in some patients that promotes suicidality and a therapeutic effect in others that alleviates depression. The age dependent increase in suicidality should be considered a phenomenon separate from therapeutic effect and approached like any other uncommon but serious adverse effect.

The possibility of separate therapeutic and adverse effects from antidepressant drugs on suicide ideation or behaviour should be the subject of further research, particularly in terms of possible mechanisms. Another possible topic for investigation would be differences among drugs.

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Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis

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ABSTRACT

Objective To assess the effect of the UK Committee on Safety of Medicines' announcement in January 2005 of withdrawal of co-proxamol on analgesic prescribing and poisoning mortality.
Design Interrupted time series analysis for 1998-2007.
Setting England and Wales.
Data sources Prescribing data from the prescription statistics department of the Information Centre for Health and Social Care (England) and the Prescribing Services Unit, Health Solutions Wales (Wales). Mortality data from the Office for National Statistics.
Main outcome measures Prescriptions. Deaths from drug poisoning (suicides, open verdicts, accidental poisonings) involving single analgesics.
Results A steep reduction in prescribing of co-proxamol occurred in the post-intervention period 2005-7, such that the number of prescriptions fell by an average of 859 (95% confidence interval 653 to 1065) thousand per quarter, equating to an overall decrease of about 59%. Prescribing of some other analgesics (co-codamol, paracetamol, co-dydramol, and codeine) increased significantly during this time. These changes were associated with a major reduction in deaths involving co-proxamol compared with the expected number of deaths (an estimated 295 fewer suicides and 349 fewer deaths including accidental poisonings), but no statistical evidence for an increase in deaths involving either other analgesics or other drugs.
Conclusions Major changes in prescribing after the announcement of the withdrawal of co-proxamol have had a marked beneficial effect on poisoning mortality involving this drug, with little evidence of substitution of suicide method related to increased prescribing of other analgesics.

INTRODUCTION

For many years concerns have been expressed about the extent of fatal poisoning with the analgesic co-proxamol, especially its use for suicide.[1 2] Between 1997 and 1999 co-proxamol was the single drug used most frequently for suicide in England and Wales (766 deaths over the three year period), implicated in nearly a fifth of all suicides from drug related poisoning.[2 3]

The Committee on Safety of Medicines (CSM) advised in January 2005 that co-proxamol should be withdrawn from use in the UK, the final date of withdrawal being 31 December 2007.[4 5] The committee also advised that during the intervening period efforts should be made to move patients to suitable alternatives.

We evaluated the effect of the announcement of co-proxamol withdrawal on prescribing and mortality involving co-proxamol and other analgesics in England and Wales. Substitution of method is a potential concern where a common means used for suicide becomes less available.[6] We therefore investigated the possible effect of the withdrawal of co-proxamol on the prescribing of other analgesics and on their use in suicide.

METHOD

Prescriptions

We obtained data on prescriptions of co-proxamol and of co-codamol, codeine, co-dydramol, dihydrocodeine, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and tramadol in England and Wales from 1998 to 2007.

Deaths

Quarterly information on deaths from drug poisoning (suicides, open verdicts, and accidental poisonings) involving co-proxamol alone, co-codamol, codeine, co-dydramol, dihydrocodeine, NSAIDs, paracetamol, and tramadol were obtained for 1998-2007 in England and Wales. We restricted our analyses to deaths involving single drugs or single drugs and alcohol. Similar data were supplied for overall drug poisoning deaths receiving suicide, open (undetermined), and accidental poisoning verdicts, and for all deaths receiving suicide and open verdicts.

In assessing whether there has been any substitution of other analgesics for co-proxamol among self-poisoning deaths we combined mortality data for all the other analgesics. We examined trends in deaths from poisoning with all drugs (suicide, open, and accidental death verdicts) and deaths from all causes (suicide and open verdicts only).

Statistical analyses

We used interrupted time series analysis to estimate changes in levels and trends in prescribing and deaths after the CSM announcement of the withdrawal of co-proxamol. This method controls for baseline level and trend when estimating expected changes in the number of prescriptions (or deaths) due to the intervention.[7]

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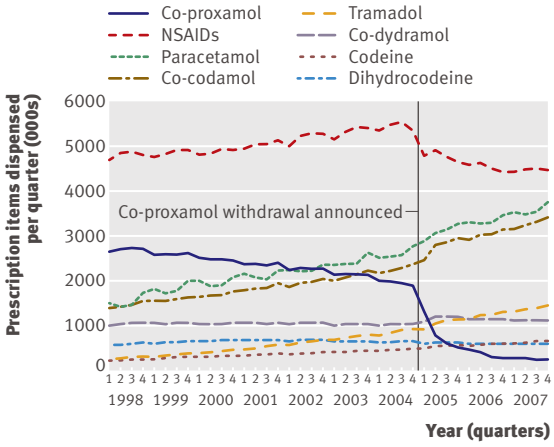
WHAT IS ALREADY KNOWN ON THIS TOPIC

In early 2005 the UK Medicines and Healthcare products Regulatory Agency announced gradual withdrawal of co-proxamol because of its adverse benefit to safety ratio, especially its use for intentional and accidental fatal poisoning
Restriction of access to dangerous means for suicidal behaviour can reduce deaths from suicide

WHAT THIS STUDY ADDS

During the three year withdrawal phase (2005-7) prescription of co-proxamol in England and Wales fell by 59%, with an increase in prescribing of some other analgesics
The marked reduction in suicides and accidental poisonings involving co-proxamol during this period, with no evidence of an increase in deaths involving other analgesics, suggests that the initiative has been effective



Prescriptions for analgesics dispensed in England and Wales, 1998-2007

Specifically, we used segmented regression analysis[8] to estimate the mean quarterly number of prescriptions and deaths that might have occurred in the post-intervention period without the CSM announcement, and the number of prescriptions and deaths that occurred with the CSM announcement. The end of 2004 was chosen as the point of intervention. Slope and level regression coefficients were used to estimate the average quarterly absolute differences.

Table 1 | Changes in prescriptions and deaths from poisoning involving co-proxamol, other analgesics, and all drugs, in England and Wales, 1998-2007, associated with the CSM announcement

	Estimation of absolute effect during 2005 to 2007 of the CSM announcement*		
	Mean quarterly estimated number without CSM announcement †	Mean quarterly estimated number with CSM announcement †	Mean quarterly change during 2005 to 2007 ‡ (95%CI) §
Prescriptions (thousands)			
Co-proxamol	1465.1	605.7	−859 (−1065 to −653)
Co-codamol	2524.7	3024.6	500 (459 to 540)
Codeine	534.6	578.0	43 (31 to 55)
Co-dydramol	1018.2	1140.0	122 (99 to 145)
Dihydrocodeine	634.6	600.0	−35 (−68 to −2)
NSAIDs	5633.8	4581.0	−1053 (−1186 to −920)
Paracetamol	2947.0	3330.0	382 (268 to 497)
Tramadol	1130.1	1193.9	64 (−5 to 133)
Suicide, open			
Co-proxamol	39	15	−24 (−37 to −12)
Other analgesics ¶	39	44	5 (−5 to 15)
All drugs except co-proxamol and other analgesics	204	191	−13 (−34 to 8)
All drugs	283	252	−31 (−66 to 3)
All causes	1152	1130	−22 (−89 to 45)
Suicide, open, accidental			
Co-proxamol	48	19	−29 (−42 to −17)
Other analgesics	56	60	4 (−11 to 18)
All drugs except co-proxamol and other analgesics	348	385	37 (−8 to 82)
All drugs	452	466	14 (−46 to 75)

*Using interrupted time series segmented regression analysis[18] where the intervention point is taken as the end of 2004 (the CSM announcement on the withdrawal of co-proxamol, January 2005).
†Estimated for the midpoint quarter of 2005 to 2007. See appendix for method, equation (2) or (3).
‡Absolute difference of estimated number with CSM announcement and estimated number without CSM announcement, taken at the midpoint of the post-intervention period, see appendix equation (4).
§95% confidence intervals (CI) taken from Stata results or calculated according to Zhang et al.[26]
¶Co-codamol, codeine, co-dydramol, dihydrocodeine, NSAIDs, paracetamol, and tramadol.

RESULTS

Prescriptions

Prescription data for England and Wales showed a steep reduction in prescription of co-proxamol in the first two quarters of 2005, with further reductions thereafter (figure).

Regression analyses indicated a significant decrease in both level and slope in prescribing of co-proxamol (appendix table), such that the number of prescriptions decreased by an average of 859 (95% confidence interval [CI] 653 to 1065) thousand per quarter in the post-intervention period (table 1). This change equated to an overall decrease of about 59% in the three year post-intervention period, 2005 to 2007. We also noted significant decreases in prescribing of NSAIDs of an average of 1053 (95% CI 920 to 1186) thousand per quarter, equating to an approximate 19% decrease overall for 2005 to 2007; and for dihydrocodeine of an average of 35 (95% CI 2 to 68) thousand per quarter, or approximately 6% overall for 2005 to 2007 (table 1).

Prescriptions for the other analgesics, apart from tramadol, increased significantly in the post-intervention period (table 1). On the basis of mean quarterly estimates, percentage increases over the 2005 to 2007 period were approximately 20% for co-codamol, 13% for paracetamol, 12% for co-dydramol, and 8% for codeine.

Deaths

Mortality data for England and Wales showed a marked reduction in suicide and open verdicts involving co-proxamol in the first quarter of 2005, which persisted until the end of 2007 (table 2). Before 2005 deaths due to co-proxamol alone accounted for 19.5% (95% CI 16.9 to 22.2) of all suicides by drug poisoning, whereas between 2005 and 2007 they constituted just 6.4% (5.2 to 7.5; table 2).

Regression analyses indicated a significant decrease in both level and slope for deaths involving co-proxamol which received a suicide or open verdict (appendix table), such that the number of deaths decreased by on average 24 (95% CI 12 to 37) per quarter in the post-intervention period (table 1). This equated to an estimated overall decrease of 295 (95% CI 251 to 338) deaths, approximately 62%, in the post-intervention period 2005 to 2007 compared with 1998 to 2004.

When deaths from accidental poisoning involving co-proxamol were included, there was a mean quarterly decrease of 29 (95% CI 17 to 42) deaths, which equated to an overall decrease of 349 (306 to 392) deaths, approximately 61%, in 2005 to 2007 (table 1).

There were no statistically significant changes in level or slope in the post-intervention period for deaths involving the other analgesics, for those that received a suicide or open verdict (mean quarterly change 5, 95% CI −5 to 15) and when accidental poisoning deaths were also included (mean quarterly change 4, −11 to 18).

There was a reduction during the post-intervention period in deaths (suicide and open verdicts) involving all drugs (including co-proxamol and other analgesics), with the mean quarterly change between 2005 and 2007 being −31 (95% CI −66 to 3) deaths, but this decrease did not

Table 2 | Suicide and open verdict deaths by all causes, and suicide, open verdict, and accidental deaths due to poisoning by all drugs, co-proxamol alone, and other analgesics alone (or with alcohol) in England and Wales

	All causes	All drugs		Co-proxamol alone†		Other analgesics* alone†	
	Suicide, open	Suicide, open	Suicide, open, accidental	Suicide, open	Suicide, open, accidental	Suicide, open	Suicide, open, accidental
1998	5347	1432	2250	298 (21)	354 (16)	207 (15)	283 (13)
1999	5241	1415	2298	298 (21)	359 (16)	208 (15)	280 (12)
2000	5081	1309	2147	296 (23)	345 (16)	175 (13)	229 (11)
2001	4904	1279	2181	268 (21)	322 (15)	200 (16)	262 (12)
2002	4762	1225	1984	217 (18)	265 (13)	182 (15)	237 (12)
2003	4811	1195	1844	196 (16)	226 (12)	166 (14)	237 (13)
2004	4883	1247	2007	204 (16)	249 (12)	168 (14)	232 (12)
2005	4718	1154	1927	70 (6)	86 (5)	183 (16)	238 (12)
2006	4513	979	1822	69 (7)	83 (5)	200 (20)	287 (16)
2007	4322	888	1852	53 (6)	63 (3)	151 (17)	209 (11)

*Co-codamol, codeine, co-dydramol, dihydrocodeine, NSAIDs, paracetamol, tramadol.
†Percentage of all drug poisoning deaths shown in brackets.

reach conventional levels of statistical significance (table 1). The mean quarterly change in the overall suicide rate (including open verdicts) was −22 (95% CI −89 to 45).

DISCUSSION

After the announcement of the withdrawal of co-proxamol in January 2005 there was an immediate large reduction in prescriptions, which during the period 2005-7 amounted to 59% fewer prescriptions than expected on the basis of data for 1998-2004. This decrease was associated with a 62% reduction in deaths from suicide related to co-proxamol, or an estimated 295 fewer deaths. Inclusion of accidental deaths increased the estimated reduction in number of deaths to 349 over three years. This level of effect was consistent with that found in Scotland during 2005-6[9] and with benefits found with prescribing restrictions in other countries in Europe.[10 11]

Although prescribing of co-codamol, paracetamol, and co-dydramol increased during 2005-07, analyses of suicides and open verdict deaths involving other analgesics combined indicated little evidence of substitution of suicide method. Since poisoning deaths with co-proxamol also often involve other substances, but co-proxamol is usually the fatal agent,[12] the overall number of deaths prevented by the CSM initiative was probably considerably greater than the figures we have reported, as we restricted our analysis to overdoses of single medicines.

Overall suicide and open verdict deaths decreased in England and Wales during 2005 to 2007 but the change was not statistically significant. Also the proportionate decline was much greater and statistically significant for co-proxamol. Thus underlying downward trends in suicide cannot account for the full extent of the decrease in co-proxamol related deaths.

Strengths and limitations

We used national data, and restricted the analyses to deaths involving single analgesics to eliminate the possible contribution of other drugs to the deaths. We also investigated possible substitution of method of suicide. We did not examine possible substitution with entirely different methods of suicide.

Our method of statistical analysis—interrupted time series autoregression—controls for baseline level and trend when estimating expected changes due to the intervention. However, the estimates of the overall effect on prescriptions and mortality involved extrapolation, which is inevitably associated with uncertainty. Also the regression method assumes linear trends over time, and the co-proxamol prescribing data, in particular, had a poor fit, resulting in large standard errors in the post-intervention period. Estimates of percentage changes over the three year post-intervention period are point estimates and were not determined with standard error calculations. Therefore caution must be advised in interpreting these percentages too literally.

Conclusions

The announcement of the withdrawal of co-proxamol in the UK has had a substantial effect on prescribing and on deaths from poisoning in England and Wales, particularly suicides. This evidence, along with a similar finding for Scotland,[12] suggests that the UK initiative has been an effective measure.

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Five year prognosis in patients with angina identified in primary care: incident cohort study

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ABSTRACT

Objective To ascertain the risk of acute myocardial infarction, invasive cardiac procedures, and mortality among patients with newly diagnosed angina over five years.

Design Incident cohort study of patients with primary care data linked to secondary care and mortality data.

Setting 40 primary care practices in Scotland.

Participants 1785 patients with a diagnosis of angina as their first manifestation of ischaemic heart disease, 1 January 1998 to 31 December 2001.

Main outcome measures Adjusted hazard ratios for acute myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, death from ischaemic heart disease, and all cause mortality, adjusted for demographics, lifestyle risk factors, and comorbidity at cohort entry.

Results Mean age was 62.3 (SD 11.3). Male sex was associated with an increased risk of acute myocardial infarction (hazard ratio 2.01, 95% confidence interval 1.35 to 2.97), death from ischaemic heart disease (2.80, 1.73 to 4.53), and all cause mortality (1.82, 1.33 to 2.49). Increasing age was associated with acute myocardial infarction (1.04, 1.02 to 1.06, per year of age increase), death from ischaemic heart disease (1.09, 1.06 to 1.11, per year of age increase), and all cause mortality (1.09, 1.07 to 1.11, per year of age increase). Smoking was associated with subsequent acute myocardial infarction (1.94, 1.31 to 2.89), death from ischaemic heart disease (2.12, 1.32 to 3.39), and all cause mortality (2.11, 1.52 to 2.95). Obesity was associated with death from ischaemic heart disease (2.01, 1.17 to 3.45) and all cause mortality (2.20, 1.52 to 3.19). Previous stroke was associated with all cause mortality (1.78, 1.13 to 2.80) and chronic kidney disease with death from ischaemic heart disease (5.72, 1.74 to 18.79). Men were more likely than women to have coronary artery bypass grafting or percutaneous transluminal coronary angioplasty after a diagnosis of angina; older people were less likely to receive percutaneous transluminal coronary angioplasty. Acute myocardial infarction after a diagnosis of angina was associated with an increased risk of death from ischaemic heart disease and all cause mortality (8.84 (5.31 to 14.71) and 4.23 (2.78 to 6.43), respectively). Neither of the invasive cardiac procedures significantly reduced the subsequent risk of all cause mortality.

Conclusions In this sample of people with incident angina from primary care, there were sex differences in survival and age and sex differences in the provision of revascularisation after a diagnosis. Acute myocardial infarction after a diagnosis of angina was strongly predictive of mortality. To minimise adverse outcomes, optimal preventive treatments should be used in patients with angina.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The findings of prognostic studies of angina in secondary or tertiary care populations might not be transferable to primary care, and primary care populations have been insufficiently researched

In trial populations, the value of percutaneous transluminal coronary angioplasty in people with angina alone is uncertain

WHAT THIS STUDY ADDS

In patients with angina in primary care there is a significant association between male sex and subsequent acute myocardial infarction, death related to heart disease, or death from any cause

Prevention of subsequent acute myocardial infarction is important in patients diagnosed with angina to avoid a significantly increased risk of death

Neither coronary artery bypass grafting nor percutaneous transluminal coronary angioplasty was associated with a significantly reduced five year risk of death among patients with angina.

Linked primary and secondary care clinical datasets provide an important opportunity to conduct studies of prognosis quickly and cost effectively

INTRODUCTION

Understanding the risk of acute myocardial infarction, invasive cardiac procedures, and death after a diagnosis of angina is important for patients and their clinicians, especially those working in primary care, where most cases of angina are first detected. Most previous studies of the prognostic importance of angina have examined populations identified from secondary or tertiary care settings. We examined the risk of several cardiac outcomes during the first five years after a first diagnosis of angina in a population identified from primary care in Scotland.

METHODS

Sampling frame

The sampling frame for the study was all patients registered with 40 practices in Scotland. In May 2007 the primary care patient data were linked with deprivation score (Scottish index of multiple deprivation), secondary care data held on the Scottish morbidity record, and cause of death data, to create a novel linked research database. The patients within the linked database are broadly representative of the Scottish population with respect to age, sex, and social deprivation.

Incident sample

From the linked database we identified everyone with a diagnosis of angina pectoris for the first time between 1 January 1998 and 31 December 2001, the index episode. We checked every identified patient's entire available general practice electronic record for any record of ischaemic heart disease, atrial fibrillation, or heart failure before the date of the index episode. We also checked the secondary care information for each person to see whether there was a diagnosis of ischaemic heart disease back to 1981. We excluded individuals with a relevant primary or secondary care diagnosis recorded before the index episode. Those without such a record were deemed to have experienced an incident (first ever) episode of angina on the index date.

The general practice computer records of incident cases were examined for the presence of "baseline" comorbidities, which were determined a priori as being related to outcome: diabetes, peripheral vascular disease, chronic kidney disease, stroke, and hypertension. We also examined the cohort for previous or subsequent recording of undefined chest pain or receipt of an angina related prescription. Similarly, the presence or absence of cardiovascular risk factors, current smoking, and being obese (defined as body mass index >30) before or after the date of the index episode of angina was ascertained by using the information closest to that date. We excluded those in whom smoking status and body mass index (BMI) were not recorded to avoid the effect of reporting bias in the analysis. The postcode of each patient was used to assign a deprivation status.

Follow-up

Each patient was followed up to the event of interest, death, or for five years (1826 days) from the date of the index episode of angina, whichever came first. The outcome measures were a record for acute myocardial infarction, revascularisation by coronary artery bypass grafting, percutaneous transluminal coronary angioplasty with or without stents, a record of death from ischaemic heart disease, and death from any cause.

Statistical analysis

We used Student's *t* tests and χ^2 tests to compare continuous and categorical variables. Survival analysis was conducted to investigate the effect of different baseline characteristics on the time to the different outcomes. Cox proportional hazards models were fitted to calculate hazard ratios for each baseline variable with adjustment for other confounding variables (sex, age, deprivation, smoking, obesity, and comorbidity at baseline). We examined the effect on future risk of death of having an acute myocardial infarction or a cardiac procedure, or both, after the index diagnosis by including these variables as additional time varying covariates in an extension of the adjusted mortality analyses. Kaplan-Meier curves displayed the probability of survival over the study period among men and women of different ages. See bmj.com.

RESULTS

Among the 40 practices, 6676 patients had angina pectoris recorded between 1 January 1998 and 31 December 2001. After exclusions, 1785 patients had a first episode of angina as a first manifestation of ischaemic heart disease and had complete data. Of these, 326 patients (157 women) had a general practice record of undefined chest pain before the index episode of angina. Five hundred and eighty four patients (296 women) had chest pain recorded after their index angina episode; 482 (82.5%) also had a subsequent general practice record of angina (246 women) and 538 (92.1%) had a subsequent record of an ischaemic heart disease condition (273 women). Forty six patients had a record of unspecified chest pain but no specific coding for ischaemic heart disease after entry into the cohort. Of these, 33 received prescriptions for angina related drugs (nitrates, β blockers, or antiplatelets), six (0.3% of the cohort) died without any subsequent treatment for ischaemic heart disease during follow-up, and seven (0.4%) who lived beyond five years were without any codes for ischaemic heart disease or prescribing data related to angina after the initial diagnosis.

The cohort included 846 (47.4%) women and 939 (52.6%) men. The mean age at cohort entry was 62.3 (SD 11.3). Women were significantly older than men (mean age at entry 63.6 (SD 11.3) *v* 61.2 (SD 11.2); $t=4.4$; $P<0.001$) and were more likely to have hypertension and be obese, while men were more likely to have had a previous stroke.

Within the five year follow-up, 152 (8.5%) patients underwent coronary artery bypass grafting, 108 (6.1%) underwent percutaneous transluminal coronary angioplasty, 116 (6.5%) an acute myocardial infarction, 84 (4.8%) died from ischaemic heart disease, and 175 (9.8%) died from any cause. All of the events were more common in men than women. A fairly consistent pattern emerged of events occurring more often among individuals with a history of comorbidity, although many of the differences were not significant.

The likelihood of having a coronary procedure remained significantly higher in men than in women even after we allowed for differences in the baseline characteristics. Older age was associated with a reduced likelihood of having a percutaneous transluminal coronary angioplasty. None of the other baseline characteristics were significantly associated with likelihood of receiving either cardiac procedure. In those patients who received the procedures, the median (interquartile range) times to coronary artery bypass grafting and percutaneous transluminal coronary angioplasty were 436.5 (201.0-836.5)

days and 218.5 (78.5-508.0) days, respectively.

Male sex, older age, and smoking were associated with an increased likelihood of having an acute myocardial infarction. In those patients who experienced an acute myocardial infarction during the study period, the median (interquartile range) time to event was 225.5 (7.0-750.0) days.

Male sex, older age, smoking and obesity were each associated with a significant increased risk of death from ischaemic heart disease or any cause (table). See bmj.com for Kaplan-Meier curves for all cause mortality in men and women stratified by age. After adjustment for baseline characteristics, a history of chronic kidney disease before the index episode was associated with an increased risk of death from ischaemic heart disease, and history of stroke with all cause mortality. Among those who died, the median (interquartile range) time to death from ischaemic heart disease was 842.5 (417.0-1179.0) days and to any death 771.0 (417.0-1193.0) days.

We found significant hazard ratios associating acute myocardial infarction after a diagnosis of angina with an increased likelihood of subsequent death from ischaemic heart disease (8.84, 95% confidence interval 5.31 to 14.71) and all cause mortality (4.23, 2.78 to 6.43). The hazard ratio associated with coronary artery bypass grafting after index diagnosis was 0.49 (0.25 to 1.95) for death from ischaemic heart disease and 0.58 (0.25 to 1.32) for all cause mortality. The corresponding figures for percutaneous transluminal coronary angioplasty after index diagnosis were 0.45 (0.13 to1.52) and 0.55 (0.22 to 1.38), respectively.

DISCUSSION

Several baseline characteristics in people with a first diagnosis of angina are associated with subsequent risk of a number of cardiac outcomes. These characteristics include (depending on outcome examined) male sex, age, smoking, obesity, and previous stroke or chronic kidney disease. An acute myocardial infarction after the index episode of angina greatly increased the risk of subsequent death. Although there was a suggestion that both coronary artery bypass grafting and percutaneous transluminal coronary angioplasty after a diagnosis of angina might reduce the subsequent risk of death from ischaemic heart disease or all cause mortality, none of the risk estimates reached significance.

Strengths and implications

A major strength was the use of a large incident cohort of patients identified in primary care and thus not prone to the selection biases that can occur through the referral process. Other strengths were the relatively long follow-up, the availability of data on several characteristics of individuals before the index diagnosis, and the novel database linkage, which allowed the use of data recorded in secondary as well as primary care and data on cause of death. The case finding method used seems robust: of the patients included in the cohort because of a first record of angina, fewer than 1% had no subsequent record of angina, another ischaemic heart disease diagnosis, or treatment related to angina.

In comparison with a cohort of patients with angina identified from secondary care cardiology clinics for the large Euro Heart cohort,[1] our cohort was slightly older and had proportionally fewer men. Our comorbidity profile was also different. Another large global cohort of patients with stable angina from a cardiac clinic (the ACTION trial), which has subsequently been used to calculate an angina risk score, had a high proportion of men.[2] These differences emphasise the need to be cautious when extrapolating findings from secondary to primary care, for instance when developing risk scores or guidelines. See bmj.com for more comparisons with these cohorts.

We found that male sex was associated with an increased likelihood of receiving either coronary artery bypass grafting or percutaneous transluminal coronary angioplasty after index diagnosis. Other studies have

Proportions and unadjusted and adjusted hazard ratios for mortality by baseline characteristics

	Ischaemic heart disease mortality			All cause mortality		
		Hazard ratio (95% CI)			Hazard ratio (95% CI)	
Baseline characteristic	No (%)	Unadjusted	Adjusted	No (%)	Unadjusted	Adjusted
Men (*v* women†)	62 (6.6)	2.40 (1.50 to 3.85)***	2.80 (1.73 to 4.53)***	110 (11.7)	1.57 (1.16 to 2.14)**	1.82 (1.33 to 2.49)***
Increasing age (per year)	71.5 (62-77)‡	1.07 (1.04 to 1.09)***	1.09 (1.06 to 1.11)***	71 (61-77)‡	1.07 (1.05 to 1.09)***	1.09 (1.07 to 1.11)***
Deprivation fifth (*v* 1st)§:						
2nd	15 (4.5)	1.57 (0.61 to 4.05)	1.41 (0.54 to 3.66)	33 (9.9)	1.09 (0.62 to 1.92)	0.97 (0.55 to 1.71)
3rd	19 (4.3)	1.51 (0.60 to 3.78)	1.50 (0.60 to 3.78)	40 (9.1)	1.00 (0.58 to 1.73)	0.96 (0.56 to 1.67)
4th	25 (6.1)	2.17 (0.89 to 5.28)	2.22 (0.91 to 5.45)	44 (10.8)	1.20 (0.70 to 2.06)	1.22 (0.71 to 2.10)
5th	21 (5.4)	1.90 (0.77 to 4.72)	1.91 (0.76 to 4.79)	39 (10.0)	1.12 (0.65 to 1.93)	1.08 (0.62 to 1.89)
Comorbidity (yes *v* no):						
Diabetes	10 (5.4)	1.13 (0.59 to 2.19)	0.97 (0.49 to 1.91)	19 (10.3)	1.05 (0.65 to 1.69)	0.92 (0.57 to 1.50)
CKD	3 (21.4)	4.81 (1.52 to 15.21)**	5.72 (1.74 to 18.79)**	3 (21.4)	2.32 (0.74 to 7.28)	2.82 (0.88 to 8.98)
Stroke	12 (10.1)	2.43 (1.32 to 4.48)**	1.80 (0.96 to 3.38)	23 (19.3)	2.28 (1.47 to 3.53)***	1.78 (1.13 to 2.80)*
PVD	8 (7.3)	1.59 (0.77 to 3.30)	0.85 (0.40 to 1.79)	17 (15.6)	1.67 (1.02 to 2.76)*	1.01 (0.60 to 1.68)
Hypertension	30 (5.1)	1.09 (0.70 to 1.70)	1.01 (0.63 to 1.61)	59 (10.0)	1.03 (0.76 to 1.41)	0.91 (0.66 to 1.27)
Smoker (yes *v* no)	34 (5.5)	1.26 (0.82 to 1.94)	2.12 (1.32 to 3.39)**	67 (10.8)	1.19 (0.88 to 1.62)	2.11 (1.52 to 2.95)***
Obese (yes *v* no)	19 (5.6)	1.24 (0.75 to 2.07)	2.01 (1.17 to 3.45)*	41 (12.1)	1.34 (0.95 to 1.90)	2.20 (1.52 to 3.19)***

CKD=chronic kidney disease; PVD=peripheral vascular disease.
*P<0.05; **P<0.01; ***P<0.001.
†24 (2.8%) women died from coronary heart disease and 65 (7.7%) died from any cause.
‡Median (interquartile range) ages of outcome.
§In first fifth of deprivation 6 (2.9%) died from coronary heart disease and 19 (9.1%) from any cause.

shown sex based differences in service provision for cardiac patients.[3 4] The different sex profile of our primary care cohort compared with the secondary care based ACTION and Euro Heart populations might also indicate that more men than women diagnosed with angina are referred to secondary care, resulting in women being more likely to be managed solely in primary care.

Neither coronary artery bypass grafting nor percutaneous transluminal coronary angioplasty was associated with significantly improved survival. The findings relating to these interventions were based on a relatively small amount of data and thus might have lacked statistical power. In addition, the observational results might have been affected by unmeasured confounding. However, the findings are in line with evidence that suggests these interventions do not confer the same survival benefits for all patients with ischaemic heart disease and that, for some, optimal medical treatments may confer similar benefits.[5-9]

Study limitations

We studied only individuals who had a recorded diagnosis of angina on their general practice records; others have already shown that women with previously unrecorded angina have an increased risk of death compared with those without such a history.[9] We did not have any details of the criteria used by the general practitioners when recording an episode of angina or of any investigations used to make the diagnosis. We did not control for treatments after diagnosis because data were not available about contraindications, severity of illness, and patients' preferences or adherence to treatments, all of which contribute to prescribing patterns and prognostic risk. It is possible that practices that contribute data to clinical databases, such as ours provide a different level of care from those that do not. If so, this could have important implications for the generalisability of our results.

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How did he learn to speak Russian?

At the international congress conference dinner, the seating plan had been really mixed. Opposite me sat a husband and wife from the United States. This was their second visit to Europe. Small talk? Not much and exhausted before the soup. On my left was a softly spoken, elderly German whose English was hard work, bearing in mind that my German was non-existent: niceties were over before the soup. On my right sat a Russian who, I surmised, had to be reasonably fluent in the conference language, English. Perhaps intimidated by the Americans nearby, she seemed to have shut down into repressive regime mode—silent, unmoving, expressionless.

The Americans had little curiosity for a gathering of once Cold War enemies, albeit under the guise of medicine, able to converse freely and openly in splendid medieval surroundings. As I tucked into the soup, left and right began to conduct a conversation in Russian. Pondering how my neighbour came to speak fluent Russian but only rather halting English despite his obvious diplomatic talents, I felt the meal turning into a drudge: better had I moved out of the way.

With the main course, the German quietly and laboriously began to explain about the Russian. She was in something akin to a state of shock. The freedom to travel to see what the rest of the world was up to had smashed the ingrained, carefully manufactured and crafted propaganda illusions of superiority in her system for government, education, agriculture, and health care. She inhabited a lie and represented in reality a Third World nation, not a superpower. She had nothing to contribute—only disappointment and shame to take back.

So, how had my neighbour learnt such fluent Russian? Was he East German? No, he was West German. Dessert, coffee, speeches, the coach trip, and late into the night in the hotel bar passed with me barely saying a word and missing everything but his story. One day in Königsberg in 1945 on his way to school, he had been picked up. He vanished. The next whole year was spent in a small cell as a prisoner in a Soviet interrogation centre. His neighbours died or, if they didn't, played chess with pieces made out of chewed bread (easily hidden and replaced). The Red Cross found him in 1955 in a Gulag prison camp after Chancellor Adenauer had negotiated with Krushchev for the repatriation of any Germans still incarcerated from the second world war and reunited him with his mother. He had learnt Russian to survive.

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Prevalence and structural correlates of gender based violence among a prospective cohort of female sex workers

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ABSTRACT

Objective To examine the prevalence and structural correlates of gender based violence against female sex workers in an environment of criminalised prostitution.
Design Prospective observational study.
Setting Vancouver, Canada during 2006-8.
Participants Female sex workers 14 years of age or older (inclusive of transgender women) who used illicit drugs (excluding marijuana) and engaged in street level sex work.
Main outcome measure Self reported gender based violence.
Results Of 267 female sex workers invited to participate, 251 women returned to the study office and consented to participate (response rate of 94%). Analyses were based on 237 female sex workers who completed a baseline visit and at least one follow-up visit. Of these 237 female sex workers, 57% experienced gender based violence over an 18 month follow-up period. In multivariate models adjusted for individual and interpersonal risk practices, the following structural factors were independently and significantly correlated with violence against female sex workers: homelessness; inability to access drug treatment; servicing clients in cars or public spaces; prior assault by police; confiscation of drug use paraphernalia by police without arrest; and moving working areas away from main streets owing to policing.
Conclusions Our results demonstrate an alarming prevalence of gender based violence against female sex workers. The structural factors of criminalisation, homelessness, and poor availability of drug treatment independently correlated with gender based violence against street based female sex workers. Socio-legal policy reforms, improved access to housing and drug treatment, and scale up of violence prevention efforts, including police-sex worker partnerships, will be crucial to stemming violence against female sex workers.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Gender based violence has been identified as a global public health and human rights priority, and leads to high morbidity and mortality
A recent review of gender based violence highlighted how rights violations and abuses against female sex workers are seldom considered in discussions of violence against women
There is a growing body of qualitative evidence documenting the adverse effects of street policing strategies on the health and safety of sex workers

WHAT THIS STUDY ADDS

Homelessness and inability to access drug treatment were independently correlated with gender based violence against female sex workers, even after adjustment for potential confounding individual and interpersonal risk factors
This study is among the first epidemiological investigations to demonstrate an independent association between criminalisation of and enforcement based approaches to sex work and raised odds of both physical and sexual violence against female sex workers
Our findings support global dialogues on preventative approaches to sex work, including removing criminal sanctions that target female sex workers

INTRODUCTION

Rights violations and abuses experienced by female sex workers are seldom considered in discussions of violence against women, as shown by a review of the global scope and magnitude of gender based violence.[1] Gender based violence has been identified as a global public health and human rights priority that leads to high rates of morbidity and mortality[2-4]; however, to date our understanding of gender based violence has been largely derived from data on partner violence.[1 3 4]

Many countries, including Canada and the UK, promote conflicting sex work regulations that maintain the buying and selling of sexual services as legal, but criminalise soliciting for sexual services in public spaces, living off the benefits of prostitution, and working indoors in managed or cooperative settings (for example, brothels).[5-8] Enforcement of these criminal sanctions has been shown to create "tolerance zones" in outlying and isolated public spaces that are then subject to police crackdowns and unwritten rules of engagement between police, clients, and sex workers. In Canada over the past two decades, urban centres have experienced epidemics of violence against sex workers that are posited to coincide with prohibitive policy changes and enforcement based approaches such as police crackdowns.[9-11] Furthermore, qualitative evidence has documented the adverse impact of street policing strategies on the health and safety of female sex workers.[12-15] There has been no empirical investigation evaluating the relation of criminalisation and enforcement based policing strategies with the likelihood of violence against female sex workers.

This study aims to identify the prevalence and structural correlates of violence against female sex workers by using longitudinal data derived from a prospective cohort of street based female sex workers in Vancouver, Canada. Three separate violence experiences—physical, sexual, and client perpetrated—were modelled separately.

METHODS

The Maka Project is a community based HIV prevention research partnership that has been described in detail elsewhere.[16] Between 2006 and 2008, street based female sex workers were enrolled in an open prospective cohort and participated in baseline and six monthly follow-up visits that included an interview questionnaire and voluntary screening for HIV. See bmj.com.

At baseline and follow-up visits, peer researchers (former and current female sex workers) administered a semistructured questionnaire about demographics, health service use, working conditions, violence, and sexual and drug risk practices. In addition, voluntary HIV screening was conducted.

Modelling

Dependent variables

Serial measures over three follow-up visits were available. The following three categories of violence experiences perpetrated by men were considered at each six month interval and modelled separately: (*a*) physical violence; (*b*) rape; and (*c*) client perpetrated violence. See bmj.com.

Independent variables

Specific environmental and structural factors collected at baseline and follow-up visits were considered on the basis of evidence in the literature and relationships hypothesised a priori. These factors were: homelessness; having tried but been unable to access drug treatment; place of servicing client; and current and historical street policing strategies. Current policing variables (reported at baseline and at each six monthly follow-up visit) included confiscation of drug use paraphernalia without arrest and moving working areas away from main streets as a result of policing. Historical police assault was recorded as self reported police assault before first baseline visit (defined as self reported physical assault and/or having been forced to provide sexual favours to police). Individual variables considered as potential confounders included age; ethnicity; HIV antibody status; drug use patterns; and Aboriginal ethnicity.

Five risky interpersonal practices were also considered as potential confounders: (*a*) having a male sex partner who injects drugs; (*b*) exchanging sex while high on injection or non-injection drugs; (*c*) having unprotected sex; (*d*) being pressured into sex (vaginal or anal) without a condom; and (*e*) having a male intimate partner who procures drugs for use by the sex worker.

Statistical analyses

Analyses were restricted to female sex workers who attended a baseline visit and at least one follow-up visit. We examined bivariate associations and tested for potential collinearity or effect modification of individual, interpersonal, and environmental and structural variables with experiences of each type of violence by using generalised estimating equations and a working correlation matrix. We used generalised estimating equations for binary outcomes, with logit link for the analyses of correlated data because the factors potentially associated with violence during follow-up were serial (time dependent) measures. We fitted separate multivariate logistic generalised estimating equation models for each of the three violence outcomes (physical violence, rape, and client perpetrated violence), adjusting for known or potential individual and interpersonal confounders and variables that retained significance with violence in bivariate analyses at $P<0.10$. See bmj.com.

RESULTS

Of 267 female sex workers invited to participate, 251 consented to participate (response rate 94%). A total of 237 women completed a baseline visit and at least one follow-up visit, with a total of 575 observations available over three visits (median visits 2, interquartile range (IQR) 2-3). Approximately half (113/237 (48%)) of the women self identified as Aboriginal and 43% (102/237) as white. The median age at baseline was 36 years (25-41 years) and the median age of sex work initiation was 15 years (13-21 years). Twenty per cent (47/237) were young women aged less than 24 years. The prevalence of HIV infection was 23% (55/237). The majority of women (206/237 (87%)) reported "absolute homelessness" (living on the street) at least once in their lifetime, with approximately half (104/237 (48%)) reporting homelessness over the 18 months of follow-up. One fifth (47/237) reported having tried but been unable to access drug treatment, with long waiting lists being the primary reason for inability to access drug treatment (45/47 (96%)). One fifth (48/237) reported one or more dependent children (median 2, IQR 1-3), with 32% (76/237) reporting having had at least one child apprehended by social welfare services (median 3, IQR 1-4).

A total of 57% (136/237) of women experienced violence at least once over the 18 month follow-up period, with 38% (90/237) reporting physical violence, 25% (60/237) rape, and 30% (70/237) client perpetrated violence.

The table shows the unadjusted and adjusted associations in the multivariate models for physical violence. Tables for rape and client perpetrated violence are shown on bmj.com. In multivariate models that adjusted for individual and interpersonal risk practices, the environmental and structural factors independently associated with violence against female sex workers were homelessness (adjusted odds ratio for physical violence (aORpv) 2.14, 95% CI 1.34 to 3.43; adjusted odds ratio for rape (aORr) 1.73, 1.09 to 3.12), inability to access drug treatment (aORpv 1.96, 1.03 to 3.43; adjusted odds ratio for client perpetrated violence (aORcv) 2.13, 1.26 to 3.62), servicing clients in cars or public spaces (aORcv 1.50, 1.08 to 2.57), prior assault by police (aORr 2.61, 1.32 to 5.16; aORcv 3.45, 1.98 to 6.02), confiscation of drug use paraphernalia by police without arrest (aORpv 1.50, 1.02 to 2.41), and moving working areas away from main streets owing to policing (aORcv 2.13, 1.26 to 3.62).

DISCUSSION

Our results demonstrate an alarming prevalence of gender based violence among a sample of street based female sex workers. We found that the environmental and structural factors of homelessness, inability to access drug treatment, servicing clients in cars or public spaces, and enforcement based policing strategies were independently associated with gender based violence, even after adjustment for the potential confounding effects of individual and interpersonal risk practices.

Comparison with other studies

The persistent relation between enforcement, both of policies on prostitution and those on drug use, and violence against female sex workers points to the role of criminalisation in enhancing the likelihood of violence against street based female sex workers. Of particular concern, prior assault by police had the strongest correlation with both sexual and client perpetrated violence against female sex workers. In 2000, the World Health Organization classified police officers' excessive use of force as a form of violence,[17] and yet there is scant empirical evidence with which to characterise the public health impact of police violence.[18 19] A growing body of qualitative evidence documents the multitude of negative outcomes of street policing strategies for female sex workers.[8-15 19] It also suggests that prior police perpetrated assault could increase fear of violence among female sex workers and reduce the likelihood they will access police and judicial support.[14]

We found an inability to access drug treatment was associated with a twofold increase in the odds of both physical and client perpetrated violence. This research suggests that the failure of the current drug strategy to support women's ability to access treatment may compound experiences of violence among female sex workers.[13]

Furthermore, the extremely high prevalence of rape experienced by female sex workers over the 18 month follow-up period points to the immediate need to scale up violence prevention strategies, including increased support for female sex workers accessing legal and victim services and improving the monitoring of and legal responses to violence against female sex workers. Preventive strategies for sexual violence also need to be integrated into HIV prevention efforts, including gender transformative and couple focused prevention.

Finally, the relation between living on the street and the enhanced likelihood of both rape and physical violence highlights the need for structural responses that focus on poverty and housing. Our findings are consistent with previous studies demonstrating an increased likelihood of physical violence among homeless women in substance using populations.[20]

Strengths and limitations

Although the observational nature of this research precludes determining causality, our longitudinal analyses using generalised estimating equations and accounting for repeated responses by the same respondent may have reduced some potential temporal bias. Additionally, the use of self reports to measure violence episodes could be subject the data to social desirability or response bias. Given the highly stigmatised and criminalised nature of sex work and our qualitative work to date, under-reporting of violence episodes would be more likely than over-reporting. Thus any misclassification would have attenuated estimates towards the null. In qualitative work, however, we have shown that physical violence perpetrated by clients is so commonplace that many women only define "bad dates" as episodes of extreme violence, such as rape. Nevertheless, we cannot discount the possibility that some variables could be over-reported. Furthermore, there are always limitations to measuring police violence as it is not possible to distinguish between excessive use of force and legitimate use of force. Finally, it might not be possible to generalise our results to other sex work environments or countries.

Conclusions

Our findings document an extremely high prevalence of both sexual and physical violence against female sex workers that persists because of large scale structural inequities. This research provides important empirical evidence demonstrating the adverse public health effects of enforcement based policing approaches to sex work and drug use. Furthermore, our findings suggest that evidence based structural interventions that promote improved access to housing and increased availability of drug treatment will be crucial to stemming the epidemic of violence against street based female sex workers.

Bivariate and multivariate models for individual, interpersonal (partner level), and environmental and structural factors correlated with client perpetrated violence against street based female sex workers

	Client perpetrated violence during 18 months of follow-up	
	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Individual factors		
Youth (≤24 years of age)	1.42 (0.78 to 2.58)	—
Aboriginal ethnicity	0.69 (0.41 to 1.51)	—
HIV positive status	0.52 (0.27 to 1.00)	—
Cocaine injection	0.89 (0.53 to 1.52)	—
Heroin injection	1.04 (0.63 to 1.73)	—
Crystal methamphetamine use	0.69 (0.33 to 1.45)	—
Crack cocaine smoking	1.12 (0.57 to 2.24)	—
Interpersonal (partner level) factors		
Unprotected sex	1.40 (0.83 to 2.37)	—
Unprotected sex with a client†	1.98 (1.15 to 3.42)	—
Pressurised into sex without a condom	2.31 (1.45 to 3.69)*	1.85 (1.10 to 3.10)
Primary sex partner injects drugs	1.18 (0.62 to 2.23)	—
Primary partner procured drugs for female sex worker	1.23 (0.71 to 1.92)	—
Exchanged sex while high	1.10 (0.69 to 1.76)	—
Environmental and structural factors		
Homeless	1.63 (0.86 to 2.67)	—
Unable to access drug treatment	2.50 (1.46 to 4.28)*	2.13 (1.26 to 3.62)
Serviced clients in cars and public spaces	1.87 (1.16 to 3.02)*	1.50 (1.08 to 2.57)
Prior assault by police	4.16 (2.35 to 7.36)*	3.45 (1.98 to 6.02)
Police confiscated drug use paraphernalia (without arrest)	1.34 (0.89 to 2.17)	—
Moved working areas away from main streets owing to policing	2.15 (1.36 to 3.40)*	2.13 (1.26 to 3.62)

*Significant at P<0.10 and entered into the multivariate model.
†Variable not entered into logistic model owing to high collinearity with another variable.

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Effect of timing of first postnatal care home visit on neonatal mortality in Bangladesh: a prospective cohort study

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ABSTRACT

Objective To assess the effect of the timing of first postnatal home visit by community health workers on neonatal mortality.
Design Analysis of prospectively collected data using time varying discrete hazard models to estimate hazard ratios for neonatal mortality according to day of first postnatal home visit.
Data source Data from a community based trial of neonatal care interventions conducted in Bangladesh during 2004-5.
Main outcome measure Neonatal mortality.
Results 9211 live births were included. Among infants who survived the first day of life, neonatal mortality was 67% lower in those who received a visit on day one than in those who received no visit (adjusted hazard ratio 0.33, 95% confidence interval 0.23 to 0.46; P<0.001). For those infants who survived the first two days of life, receiving the first visit on the second day was associated with a 64% lower neonatal mortality than in those who did not receive a visit (adjusted hazard ratio 0.36, 0.23 to 0.55; P<0.001). First visits on any day after the second day of life were not associated with reduced mortality.
Conclusions In developing countries, especially where home delivery with unskilled attendants is common, postnatal home visits within the first two days of life by trained community health workers can significantly reduce neonatal mortality.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The burden of neonatal mortality is high in most developing countries

Studies suggest that postnatal home visits by trained community health workers can reduce mortality, particularly in settings where health systems are weak, but no previous studies have assessed the effect by timing of visits

WHAT THIS STUDY ADDS

Receiving a visit on the day of birth reduced the risk of neonatal mortality by two thirds among neonates who survived the first day of life

Among infants who survived the first two days of life, receiving a visit on the second day reduced the risk of neonatal mortality by 64%

No significant reduction in neonatal mortality was measured among neonates receiving the first home visit after day two of life

Home visit and assessment of neonates by a trained health worker within two days of birth should be made a priority in settings where health systems are weak and coverage of skilled birth attendance is low

INTRODUCTION

Home visits by trained community health workers to promote preventive care and to provide curative newborn care has been shown to be efficacious at

reducing perinatal and neonatal mortality. No published studies have examined the effect of the timing of postnatal home visits on neonatal mortality, however, an important question to consider when designing health programmes.

The Project for Advancing the Health of Newborns and Mothers (Projahnmo; a Bangla word that means "generation") tested two strategies—community care and home care—for delivery of a package of community based maternal and neonatal care interventions in rural northeast Bangladesh.[1] In the home care arm, community health workers made scheduled antenatal and postnatal home visits to deliver the interventions. In this analysis, we examined the effect of the timing of the first postnatal home visit on neonatal mortality.

METHODS

Data source

Projahnmo was implemented in Sylhet district, Bangladesh, which had skilled birth attendance coverage of approximately 10%, poor healthcare access, and neonatal mortality of about 48 per 1000 live births.[2] Briefly, 24 administrative units, each with a population of about 20 000 and served by a primary care centre, were randomised to home care, community care, or the comparison arm (standard care from governmental and non-governmental organisations).[1] The intervention was rolled out over six months and implemented for 24 months between January 2004 and December 2005.

In the home care arm, one community health worker was recruited for every 4000 population. Community health workers (hereafter referred to as "health workers") conducted pregnancy surveillance every two months throughout the intervention period to identify pregnant women in their catchment area. Health workers were expected to visit all pregnant women twice before birth (at 12-16 weeks and 30-34 weeks of gestation) and all newborns on the first, third, and seventh days of life. During postnatal visits, the health workers reinforced the essential newborn care messages, provided support to mothers to establish breastfeeding, assessed newborns using an algorithm adapted from the World Heath Organization's Integrated Management of Childhood Illness guidelines, referred newborns who showed signs of serious illness according to the algorithm, and delivered antibiotic injections to newborns if referral failed but parents consented to antibiotic treatment.[3 4] The content of postnatal visits was the same, regardless of timing or number of visits.

The health workers received six weeks of training. Three day refresher training was conducted midway through implementation. One field services supervisor provided ongoing training and support to six to eight health workers. Health workers also attended meetings every two weeks to review their job responsibilities and receive feedback.

Health workers in the home care arm maintained records of antenatal and postnatal visits and made a final visit to all households between day 29 and day 35 to ascertain final survival status of live born infants. Field services supervisors routinely checked health workers' records, made independent home visits to check data quality, and addressed data problems during fortnightly meetings with health workers.

Statistical methods

This analysis used data from the health workers' records. In the home care arm 97% of women received at least one antenatal home visit; so the effect of antenatal visits was not evaluated.

Neonatal mortality was calculated as the number of deaths in the first 28 days of life per 1000 live births.

Hazard ratios for neonatal mortality by day of first postnatal home visit (2004-5)

	Day of birth (hazard ratio (95% CI))	2nd day of life (hazard ratio (95% CI))	3rd-6th day of life (hazard ratio (95% CI))	≥7th day of life (hazard ratio (95% CI))
Unadjusted analysis				
Day of first postnatal visit†	0.31*** (0.22 to 0.43)	0.34*** (0.22 to 0.52)	0.39 (0.14 to 1.13)	0.87 (0.38 to 1.99)
Adjusted analysis				
Day of first postnatal visit†	0.33*** (0.23 to 0.46)	0.36*** (0.23 to 0.55)	0.60 (0.31 to 1.16)	0.88 (0.38 to 2.02)
Economic status				
Poorest	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
Middle	0.60* (0.39 to 0.92)	0.70 (0.41 to 1.19)	0.76 (0.37 to 1.55)	0.62 (0.22 to 1.71)
Least poor	0.57 (0.31 to 1.06)	0.49 (0.20 to 1.16)	0.53 (0.15 to 1.81)	1.01 (0.32 to 3.15)
Mother's education				
No education	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
1-5 years	0.76 (0.50 to 1.16)	0.90 (0.55 to 1.48)	0.91 (0.46 to 1.80)	0.70 (0.28 to 1.75)
6 or more years	0.80 (0.49 to 1.31)	0.46* (0.22 to 0.95)	0.26* (0.07 to 0.88)	0.40 (0.11 to 1.50)
First pregnancy				
No	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
Yes	1.57* (1.05 to 2.34)	1.93** (1.19 to 3.14)	1.58 (0.77 to 3.24)	1.35 (0.52 to 3.50)
Gestational age				
<37 wks	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
≥37 wks	0.34*** (0.24 to 0.48)	0.34*** (0.22 to 0.52)	0.20*** (0.11 to 0.37)	0.15*** (0.07 to 0.34)
Multiple births				
Single	1.00 (—)	1.00 (—)	1.00 (—)	1.00 (—)
Twins or triplets	3.64*** (1.95 to 6.81)	6.67*** (3.32 to 13.4)	6.24*** (2.40 to 16.2)	3.23 (0.75 to 13.9)

A newborn must have survived up to and including the day of the visit to be included in the analysis. Deaths before or on the day of the visit were excluded from each analysis.
*P<0.05; **P<0.01; ***P<0.001.
†The hazard ratio reference category for all "Day of first postnatal visit" is "No postnatal visit".

Neonatal mortality was calculated separately for newborns who received their first postnatal visit on: 1) the day of birth; 2) the second day; 3) the third, fourth, fifth, or sixth day; and 4) the seventh day or a later day of life. Infants who received their first visit during a specified time frame were compared with those who never received a visit. Survival bias is a concern in studies that examine the effect of time to treatment initiation.[5] In our study, a newborn must have survived up to and including the day of the visit to be included in the analysis.

To minimise the risk of survival bias, we fitted a time varying discrete hazards model to calculate unadjusted and adjusted hazard ratios for neonatal mortality.[5] In this model, subjects were entered conditionally in the analysis according to risk status for the specified visit.[5] The adjusted models included the following variables known to be associated with neonatal mortality: household economic status; mother's education level; primigravid status; preterm birth; and multiple gestations. The variances estimated by the model were adjusted for clustering at community level. See bmj.com for full statistical details including assessment of household economic status.

RESULTS

The prospective data showed 10 585 live births, 562 stillbirths, and 159 spontaneous or induced abortions between January 2004 and December 2005. The 1374 women who delivered in their natal home were excluded because they were not eligible for visits by health workers; therefore, 9211 live births that occurred at home or at a facility were included in this analysis.

A total of 2838 (31%) newborns received their first postnatal visit on the first day of life and 2867 (31%) received their first visit on the second day of life, whereas 983 (11%) newborns received their first visit on the third to sixth day of life, 1224 (13%) newborns received their first visit after the first week of life and 1287 (14%) newborns never received a postnatal visit. Compared with mothers who had at least one postnatal visit, mothers of neonates who received no postnatal visit had spent longer in education, were more often from wealthier households, were more likely to be primigravid, and more often had preterm deliveries. See bmj.com.

Receiving the first postnatal visit on the day of birth was associated with considerably lower neonatal mortality (20.5, 95% CI 15.6 to 26.4) than receiving no visit (65.2, 52.0 to 80.5). For those infants who survived the second day, having the first visit on that day was also associated with appreciably lower neonatal mortality (13.3, 9.4 to 18.2) than never having a visit (38.6, 28.4 to 51.1). There was no evidence for an effect of timing of first postnatal visit after the second day. When the analysis was restricted to home births only, a visit on the first day was associated with a hazard ratio for neonatal mortality of 0.30 (0.21 to 0.44) and a visit on the second day was associated with a hazard ratio of 0.35 (0.22 to 0.56).

The adjusted hazard ratios showed that neonatal mortality was 67% lower in infants who received their first postnatal visit on the day of birth compared to those who did not receive a visit (table).

One quarter (25%) of the neonatal deaths occurred on the first day of life, and these deaths were excluded to avoid survival bias. If it is assumed that the postnatal visits had no effect on deaths that occurred on the first day of life, a postnatal visit on the day of birth would be associated with approximately 50% lower overall neonatal mortality and a day two visit would be associated with 38% lower neonatal mortality.

DISCUSSION

About a third of neonatal deaths globally occur in the first 24 hours of life, and three quarters occur during the first week.[6] This analysis has demonstrated that a home visit by a trained community health worker in the first two days of an infant's life can significantly reduce neonatal mortality. We included in the analysis births that occurred either at home or at facilities because we wanted to estimate the population level effect of the programme; however, limiting the analysis to only home births did not change the findings. In a separate study, we have shown that newborns treated by health workers have treatment outcomes comparable to those treated by qualified medical providers.[4]

Comparison with other studies

Other programmes have been successful at using community based health workers and other workers with limited training to identify preterm or low birth weight infants, to manage birth asphyxia, to recognise and treat sepsis and pneumonia, and to promote use of healthcare services by mothers and newborns.[7-9]

Strengths and limitations

One advantage of this study is that the data on the timing of visits and the data on neonatal mortality were collected prospectively. This analysis also has limitations. Assignment to the group that received no postnatal home visit or the group that received visits was not randomised; however, randomisation of neonates to postnatal home visit or no visit would not be ethical. Durable household assets and housing materials have been shown to be a reasonable proxy for estimating wealth status, but our data were limited to housing materials. Selectivity bias and survival bias were concerns in this analysis; we attempted to account for these by adjusting for differences in background characteristics and by excluding deaths that occurred up to the day of visit. Another potential limitation is that the workers who delivered the intervention also collected data on outcomes; however, data quality was maintained by supervisors who conducted independent home visits. Finally, we are unable to examine the effect of the number of visits on neonatal mortality.

Conclusions and policy implications

We recommend that in developing countries, especially those where home delivery with unskilled attendants is the norm, all newborns should receive a home visit and undergo assessment by a trained worker as soon as possible, preferably on the day of birth but no later than 48 hours after birth.

The Projahnmo 1 Study Group comprised the International Centre for Diarrhoeal Disease Research, Bangladesh; the Bangladesh government's Ministry of Health and Family Welfare; Bangladeshi nongovernmental organisations, including Shimantik, Save the Children, Dhaka Shishu Hospital, and the Institute of Child and Mother Health; and the Johns Hopkins Bloomberg School of Public Health. We thank the many individuals in Sylhet district who gave their time generously, and the field and data management staff of Projahnmo. We thank the members of the Projahnmo Technical Review Committee; the Bangladesh Ministry of Health and Family Welfare colleagues at the sub-district, district, and central levels; and the members of the Shimantik executive committee, for their valuable help and advice. The critical innovative inputs of Projahnmo study group members are acknowledged. The Projahnmo Study Group includes (in alphabetical order): Jahiruddin Ahmed, Saifuddin Ahmed, Ashraful Alam, Ahmed Al-Kabir, Arif Billah Al-Mahmud, Ahmed Al-Sabir, Tariq Anwar, Nabeel Ashraf Ali, Abdullah H Baqui, Nazma Begum, Robert E Black, Atique Iqbal Chowdhury, Mohiuddin Chowdhury, Sameena Chowdhury, Gary L Darmstadt, Milan Krishna Das, Shams El-Arifeen, Zafar Ahmad Hakim, A K M Fazlul Haque, Quamrul Hasan, Daniel Hossain, Shahla Khatun, Paul Law, Amnesty LeFevre, Ishtiaq Mannan, Syed Moshfiqur Rahman, Qazi Sadequr Rahman, Samir K Saha, Mathuram Santosham, Habibur Rahman Seraji, Rasheduzzaman Shah, Ashrafuddin Siddik, Uzma Syed, Hugh Waters, Emma K Williams, Peter J Winch, and K Zaman. The study is registered as an International Standard Randomised Control Trial, number NCT00198705.

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Ethical approval: This study received ethical approval from the Johns Hopkins Bloomberg School of Public Health Committee on Human Research and the Ethical Review Committee of the International Centre for Diarrhoeal Disease Research, Bangladesh. Informed consent was obtained from all study participants. During the formative research phase, we engaged in consensus building activities with local communities to gain local support for the project.

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Caution with home fetal Doppler devices

A 27 year old presented to our labour ward at 8 pm, 32 weeks into her first pregnancy with reduced fetal movements. She had first noted a reduction in fetal activity two days earlier but had used her own Doppler device to listen to the fetal heartbeat and reassured herself that everything was normal. A fetal cardiotocograph was not reassuring and showed reduced variability for over an hour. Steroids were given to enhance fetal lung maturity, and the baby was delivered by caesarean section later that evening. The baby was floppy and small for gestational age with poor Apgar scores (3 at 1 minute, 6 at 5 and 10 minutes) and acidotic cord gases (pH 6.97, base excess −19.1). The placenta looked calcified and pale. The baby remained on the special care baby unit for eight weeks with hypoxic ischaemic encephalopathy and an intraventricular haemorrhage. The baby is now making steady progress with her neurodevelopment.

The current guidelines from the National Institute for Health and Clinical Excellence (NICE) on detection of fetal wellbeing do not support the routine counting of fetal movements, but most obstetric units would encourage patients to attend for a cardiotocograph and possibly further ultrasound assessment of growth and fetal activity if episodes of reduced movements recur. A hand-held Doppler device assesses the presence of fetal heart pulsations only at that moment, and it is used by midwives and obstetricians to check for viability or for intermittent monitoring during labour. In untrained hands it is more likely that blood flow through the placenta or the maternal aorta or iliac vessels will be heard.

An internet search revealed that a fetal Doppler device could be hired for £10 a month or bought for £25-50 (www.ebay.co.uk). Although the companies offering sales state that the device is not intended to replace recommended antenatal care, they also make claims such as "you will be able to locate and hear the heartbeat with excellent clarity" (www.hi-baby.co.uk).

Although self monitoring provided false reassurance and a delay in seeking help in this case, it is difficult to say if this altered the outcome. We now have posters in our antenatal areas to recommend that patients do not use these devices.

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Patient consent obtained.

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pico

Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomised controlled trials

FAST TRACK

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Carl Heneghan and Matthew Thompson talk about their paper in a *BMJ* podcast at podcasts.bmj.com/bmj/

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STUDY QUESTION What is the evidence for the efficacy, safety, and tolerability of neuraminidase inhibitors in the treatment and prevention of influenza in children?

SUMMARY ANSWER Neuraminidase inhibitors provide a small benefit by shortening the duration of illness in children with seasonal influenza and reducing household transmission. They have little effect on asthma exacerbations or use of antibiotics. Oseltamivir is associated with an increased risk of vomiting.

Selection criteria for studies

We identified randomised controlled trials of neuraminidase inhibitors in children aged ≤12 in the community (that is, not admitted to hospital) with confirmed or clinically suspected influenza by electronic searches of Medline and Embase to June 2009, reviewed trial registries, and contacted manufacturers and authors of relevant studies.

Primary outcome(s)

We examined time to resolution of influenza and incidence of influenza in children living in households with an index case of an influenza-like illness.

Main results and role of chance

We included four randomised trials for treatment of influenza (two oseltamivir, two zanamivir) involving 1766 children (1243 with confirmed influenza) and three randomised trials for postexposure prophylaxis (one oseltamivir, two zanamivir) involving 863 children. No trials tested efficacy for the current pandemic influenza A/H1N1 (swine flu). Neuraminidase inhibitors shortened the duration of symptoms in children with laboratory confirmed influenza by 0.5 to 1.5 days. For children with an influenza-like illness the reduction in duration of symptoms was smaller. Thirteen children would need to be treated with a 10 day course of neuraminidase inhibitors to prevent one additional case of symptomatic influenza after contact with an index case (risk difference 0.08, 95% confidence interval 0.05 to 0.12). Only one trial of oseltamivir reported on children with asthma; it showed no reduction in exacerbations or improvement in peak flow. Treatment of children aged 1-5 with oseltamivir was associated with a reduction in otitis media; neither treatment was effective in 6-12 year olds. Treatment was not associated with a reduction in overall use of antibiotics. Zanamivir was well tolerated, but oseltamivir was associated with an increased risk of vomiting, with one extra case for every 20 children treated (risk difference 0.05, 0.02 to 0.09).

Bias, confounding, and other reasons for caution

Study quality was generally moderate, partly because of poor reporting. Only one of seven included studies was rated free from bias. Reductions in duration of illness were not all significant, leaving uncertainty in both the size and confidence in these effects. We were severely hampered in our ability to aggregate results by the inconsistency of outcomes measured and the availability of data. None of the studies was sufficiently powered to determine the effects of neuraminidase inhibitors on serious complications of influenza (such as pneumonia or admission to hospital). We found no evidence in these trials on efficacy and safety in children aged under 1. The efficacy data might not be transferable to the current pandemic influenza A/H1N1.

Study funding/potential competing interests

The Department of Primary Health Care is part of the NIHR School of Primary Care Research.

MEDIAN DAYS TO RESOLUTION OF INFLUENZA SYMPTOMS IN CHILDREN WITH CONFIRMED INFLUENZA

Study	Antiviral	Control	Difference (95% CI), P value
Zanamivir			
NAI30009[w2]	4·0	5·25	1·25 (0·5 to 2·0), P<0·001
NAI30028[w1]	5·0	5·5	0.5 (NA), P=NA
Oseltamivir			
WV15758[w3]	2·6	4·2	1.5 (NA), P<0·001
WV15759/ WV15871[w4]	3·8	4·8	1.1 (NA), P=0·12

NA=not available

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Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis

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STUDY QUESTION What is the diagnostic accuracy of currently available point of care D-dimer tests, in particular for excluding venous thromboembolism in suspected outpatients?

SUMMARY ANSWER Point of care D-dimer tests can safely exclude venous thromboembolism in low risk outpatients.

Selection criteria for studies

An electronic search was performed in Medline and Embase for studies on the diagnostic accuracy of point of care D-dimer tests published between January 1995 and September 2008. Only studies investigating consecutive outpatients (age >18 years) suspected of venous thromboembolism were included in the analysis. Bivariate regression was used to examine sources of variation and to estimate sensitivity and specificity.

Primary outcome(s)

The sensitivity, specificity, and negative predictive value of point of care D-dimer tests were the primary outcomes. Predefined reference criteria for venous thromboembolism (for example, compression ultrasonography for deep vein thrombosis) were used for comparison.

Main results and role of chance

In total, 23 studies (13 959 patients) were included in the meta-analysis. The studies reported two qualitative point of care D-dimer tests—SimpliRED D-dimer (n=12) and Clearview Simplify D-dimer (n=7)—and two quantitative point of care D-dimer tests—Cardiac D-dimer (n=4) and Triage D-dimer (n=2). Overall sensitivity ranged from 0.85 (95% confidence interval 0.78 to 0.90) to 0.96 (0.91 to 0.98) and overall specificity from 0.48 (0.33 to 0.62) to 0.74 (0.69 to 0.78).

In daily practice, D-dimer testing is predominantly used to exclude the diagnosis of venous thromboembolism. We used Bayes' theorem to calculate the post-test probability of a negative point of care D-dimer test result (that is, the negative predictive value) for patients with one of three clinically relevant pre-test probabilities: low risk (5%); moderate risk (20%); and high risk (50%). Given that the false negative rate of imaging tests for venous thromboembolism is around 1-2%, any test achieving a post-test probability of 2% or less is generally accepted as safe. Applying this safety threshold, all point of care D-dimer tests were sufficiently safe in low risk patients as they achieved a post-test probability of 0.4-1.1% (table).

Bias, confounding, and other reasons for caution

Most studies assessed in this meta-analysis included patients suspected of deep venous thrombosis; therefore, the results of this meta-analysis should be interpreted with more caution when considering patients suspected of pulmonary embolism. In addition, substantial heterogeneity was found for the SimpliRED D-dimer test, probably a result of implicit threshold differences caused by low interobserver agreement for defining a positive/negative result in this test.

Study funding/potential competing interests

This study was supported by the Netherlands Heart Foundation (project number 2006B237) and "Zilveren Kruis Achmea" (project number Z195), a Dutch Health insurance company. In addition, the authors have conducted previous studies with point of care D-dimer tests and have received Clearview Simplify D-dimer, Cardiac D-dimer, and Triage D-dimer test kits free of charge for study purposes. These organisations and manufacturers, however, were in no way involved in the meta-analysis and had no influence on any aspect of this study.

NEGATIVE PREDICTIVE VALUE OF POINT OF CARE D-DIMER TESTS FOR PATIENTS AT LOW, MODERATE, OR HIGH RISK OF VENOUS THROMBOEMBOLISM

	Likelihood ratio of a negative test result (95% CI)	Post-test probability of a negative test result (95% CI)
SimpliRED D-dimer	0.21 (0.15 to 0.29)*	
Low risk		1.1 (0.8 to 1.5)
Moderate risk		4.9 (3.6 to 6.8)
High risk		17.4 (13.0 to 22.5)
Clearview Simplify D-dimer	0.22 (0.17 to 0.28)*	
Low risk		1.1 (0.9 to 1.5)
Moderate risk		5.2 (4.1 to 6.5)
High risk		18.0 (14.5 to 21.9)
Cardiac D-dimer	0.07 (0.04 to 0.16)*	
Low risk		0.4 (0.2 to 0.8)
Moderate risk		1.7 (1.0 to 3.8)
High risk		6.5 (3.8 to 13.7)
Triage D-dimer	0.18 (0.08 to 0.43)*	
Low risk		0.9 (0.4 to 2.2)
Moderate risk		4.3 (2.0 to 9.7)
High risk		15.3 (7.4 to 30.1)

Low risk=5%; moderate risk=20%; and high risk=50%.
*The likelihood ratio of a negative test result is calculated by dividing (1-sensitivity) over specificity, using the pooled estimates

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