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A systematic rapid evidence assessment of late diagnosis

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SSRU Social Science Research Unit

SUMMARY REPORT

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Conflicts of interest

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Contributions

The opinions expressed in this publication are not necessarily those of the EPPI-Centre or the funders. Responsibility for the views expressed remains solely with the authors.

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Contents

Background

Delayed diagnosis results in serious consequences for patients and healthcare professionals and has the potential to incur substantial financial costs.

There are numerous points at which a delay in diagnosis can occur: in the help-seeking behaviour of the patient; access to healthcare (waiting for an appointment); clinical assessment in primary and secondary care (not investigating or misdiagnosing); test ordering (waiting for tests); test results (test results lost or misdirected); and referral (referral waiting time, referral missed, prioritisation incorrect). Hansen et al. (2008) delineate three categories of delay in diagnosis: 'patient delay' (attributable to the patient); 'doctor delay' (attributable to clinical staff); and 'system delay' (attributable to administrative and procedural errors). There may also be time lost between diagnosis and referral to, or initiation of, treatment ('treatment delay').

Kostopoulou et al. (2008) describe common features of diagnostic difficulty including: atypical presentation; non-specific presentation; rarity of condition; the presence of co-morbidity; and perceptual features susceptible to subjective judgement. Demographic characteristics influencing delayed diagnosis include (among others) age, gender, socioeconomic status and level of education (McDonald et al. 2006, Mitchell et al. 2008, Scott et al. 2006).

While a substantial body of research focussing upon cancer suggests that late diagnosis leads to increased morbidity and mortality, the state of the evidence base for other conditions is less clear. This systematic rapid evidence assessment (SREA) has been commissioned to identify and characterise this research across a range of conditions.

Review question

What is the nature and extent of UK evidence on delayed diagnosis?

Methods

A systematic rapid evidence assessment (SREA) represents the only way in which a broad policy question may be answered within a tight timescale. A SREA was conducted in two phases. Initially, a systematic map was produced to answer the question "What is the nature and extent of UK evidence on delayed diagnosis?" The map contained a brief overall characterisation of the distribution of studies and a quality assessment of relevant systematic reviews.

The map was used to focus discussion with policy customers in order to inform decisions about policy relevant topics for the second phase: an in-depth review and synthesis of the findings of systematic reviews concerning late diagnosis in:

- chronic kidney disease,
- chronic obstructive pulmonary disease,
- dementia,
- depression,
- type I diabetes,

- epilepsy,
- HIV,
- myocardial infarction,
- psychosis,
- stroke
- tuberculosis,

A review of the results of UK primary studies examining late diagnosis in chronic obstructive pulmonary disease (COPD), tuberculosis and epilepsy was also conducted. The two types of studies included in the second phase reflected the available evidence: while there were relevant systematic reviews on which we could draw for most areas, this was not the case for COPD (no systematic reviews), tuberculosis (systematic reviews had limited relevance to UK healthcare system) and epilepsy (systematic reviews focussed upon over-diagnosis).

Each chapter was reviewed by relevant National Clinical Directors and colleagues prior to the final draft being written. Where their feedback concerned the systematic review evidence, this was incorporated directly into the syntheses; where the material went beyond the evidence supplied by the reviews (or primary studies for COPD, epilepsy and tuberculosis) and gave, for example, information that was more up to date or particularly relevant to the UK context, this is included in a 'discussion of recent research' section for each condition.

Results

The search of bibliographic databases provided a total of 28,994 citations. Sixty-seven papers were identified via experts and reference checking. After removing duplicate references, 25,799 records remained. Using text mining tools, we prioritised 18,075 (70%) records for screening. Of these, 16,818 were excluded after reviewing the abstracts because it was judged that they did not meet the eligibility criteria. Two additional studies were excluded because it was not possible to retrieve the full text of the study within the timeframe of the review.

We identified 43 systematic reviews investigating late diagnosis. UK primary studies investigating late diagnosis numbered 606, of which 12 investigated late diagnosis and COPD, 12 investigated late diagnosis and tuberculosis and 4 investigated late diagnosis and epilepsy.

A flow diagram illustrating the process of study selection throughout the review is presented in Figure 1 below. An overview of the findings of the SREA is presented in Table 1.

Figure 1: Flow of studies through the review

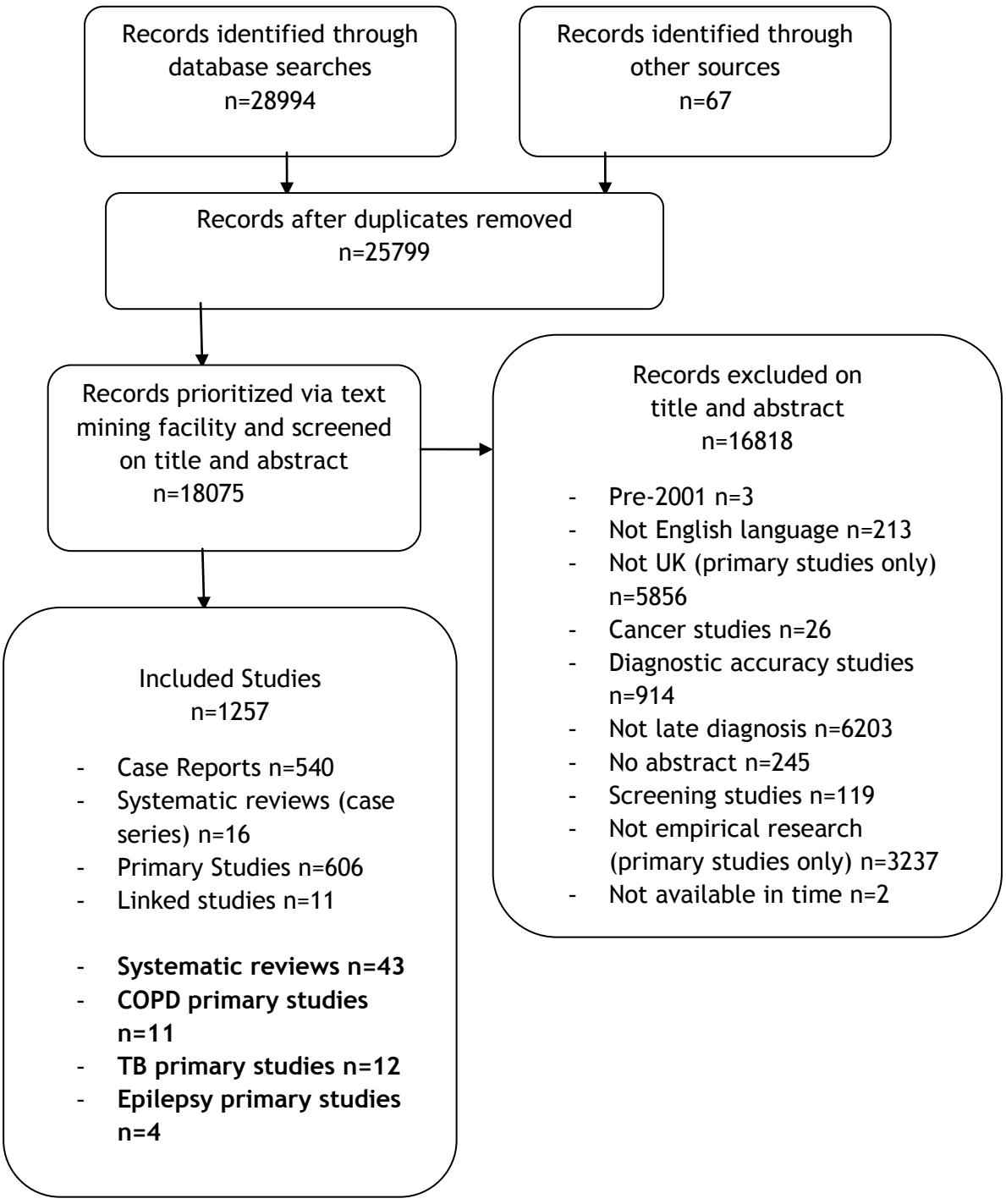

Table I: Overview of the findings of the systematic rapid evidence assessment

	CKD	COPD	Dementia	Depression	Diabetes (Type I)	Epilepsy	HIV	MI	Psychosis	Stroke	TB
Number of systematic reviews	5	0	3	3	1	0	2	6	7	4	4 (limited UK relevance)
UK primary studies	-	12	-	-	-	4	-	-	-	-	12
Metrics for late diagnosis	Stage	Stage	Severity		Keto-acidosis		CD4 count	Death	DUP	Death	
Is late diagnosis or under-diagnosis common?	~20% late referral	~80%	✓	ND	16-51%	ND	✓	ND	ND	✓	✓
Patient factors associated with late diagnosis	(Late referral)										
Age	?	Older	?	Older	<5yrs	ND	ND	? Older	ND	TIA Ø	Older
Gender	Ø	Ø	♀	ND	♀	ND	ND	♀	Ø	TIA Ø	♀
Ethnicity	Ø	ND	ND	ND	Minorities	ND	ND	Ø	Ø	ND	White
SES	?	ND	ND	ND	Lower	ND	ND	Lower	Ø	ND	Lower
Education	ND	ND	Lower	ND	Lower	ND	ND	Ø	ND	ND	Lower
Marital Status	ND	ND	Single	ND	n/a	ND	ND	Single	ND	ND	ND
Family History	Protective	ND	ND	ND	Protective	ND	ND	ND	ND	ND	ND
Location	?	Urban	Rural	ND	Ø	ND	ND	Ø	ND	ND	Rural

	CKD	COPD	Dementia	Depression	Diabetes (Type I)	Epilepsy	HIV	MI	Psychosis	Stroke	TB
Clinical Factors											
Atypical symptoms	ND	ND	ND	ND	?	ND	ND	ND	ND	ND	Extra-pulmonary
Co-morbidities	?	Asthma	Depression	ND	Infection; fever	ND	ND	Diabetes Ø Hypertension Ø	ND	ND	ND
Misattribution	ND	Asthma	Depression	ND	✓	ND	ND	ND	ND	ND	✓
Non-specific symptoms	ND	✓	Milder cases	ND	ND	ND	ND	ND	ND	ND	✓
Severity	ND	Milder cases	Milder cases; patient impair-ment	Milder cases	?	ND	ND	Milder cases	ND	ND	ND
General Practice Factors											
Knowledge / Training	Stage recog-nition; Referral criteria	Spirom-etry	✓	ND	ND	ND	ND	ND	ND	ND	✓
Clinical attitudes	ND	ND	Nihilism; fear; discomfort	ND	ND	ND	GP anxiety/ reticence	ND	ND	ND	ND
Consultation time	ND	ND	✓	ND	ND	ND	ND	ND	ND	ND	✓
Frequency of contact	ND	ND	✓	ND	ND	ND	ND	ND	ND	ND	Continuity
Communication	✓	ND	✓	ND	ND	ND	✓	ND	ND	ND	✓

	CKD	COPD	Dementia	Depression	Diabetes (Type I)	Epilepsy	HIV	MI	Psychosis	Stroke	TB
Outcomes											
Mortality	↑	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Hospital admissions / length of stay	↑ Initial stay	↑ admissions	ND	ND	ND	ND	ND	ND	ND	ND	↑ In-patient care
Morbidity	↑	↑	ND	ND	ND	↑	↑	ND	↑	ND	ND
Remission	n/a	n/a	n/a	ND	ND	↓	ND	ND	↓	ND	ND
Costs	↓ earlier referral	ND	ND	ND	ND	↑ over-diagnosis	ND	ND	ND	ND	↓ outreach service
Interventions	Early referral	Case finding	Doctor education	ND	ND	Case review	ND	Mass media campaigns; pre-hospital ECG; primary angioplasty; thrombolysis	EIS; mass media campaign	mass media camp-aign; doctor educat-ion	Reminder systems; Doctor education

CKD Chronic Kidney Disease; COPD Chronic Obstructive Pulmonary Disease; HIV Human Immunodeficiency Virus; MI Myocardial Infarction; TB Tuberculosis; TIA Transient Ischaemic Attack; SES Socio-economic status; DUP Duration of Untreated Psychosis; EIS Early Intervention Services
? = Results mixed/conflicting/unclear; Ø = no association; ND = No data; n/a = not applicable; ↓ = decrease; ↑= increase; ♀= female; ♂ = male

We present the key findings from each chapter covering the conditions reviewed. We then present the information sent to us by the National Clinical Directors (NCDs) that updates the information in the reviews and puts a UK perspective on these issues. The exceptions are dementia, where the director felt the chapter was an adequate description of the current situation in this country; and tuberculosis, where the feedback led us to synthesize current UK research, as the systematic reviews contained too much information from healthcare systems that are very different to the UK context.

Chronic Kidney Disease

We found five systematic reviews relating to delayed referral (as variously defined in individual studies) for chronic kidney disease (Black et al. 2010; Chan et al. 2007, Kahn and Amedia 2008, Navaneethan et al. 2008, Smart and Titus 2011).

The proportion of referrals occurring within four months of the need to start dialysis ranged from between 20% and 50%. Two primary studies found evidence to suggest that approximately 40% of late referrals were attributable to patient non-compliance with appointments.

There was no evidence that gender and ethnicity were associated with late referral for chronic kidney disease. It was unclear whether age, socio-economic status, co-morbidities or geographical barriers to access influenced the timing of referral.

Doctors' lack of knowledge and awareness of guidelines, inadequate training and faulty communication between primary care doctors and nephrologists were identified as barriers to early referral.

Late referral resulted in unfavourable outcomes: significantly increased mortality; a prolongation of initial hospital stay; lower uptake of peritoneal dialysis; permanent access was less likely and temporary access more likely; erythropoietin usage was lower; and serum creatinine levels were higher and haemoglobin levels were lower as compared with patients referred early to nephrology care.

There is evidence to suggest that earlier referral is associated with lower costs.

Discussion of Recent Research

Recent research from the UK indicates that late referral to nephrology is a problem that the health service is beginning to tackle. Eleven centres (Basildon, Bradford, Dorset, Leeds, Middlesbrough, Nottingham, Oxford, Portsmouth, Sheffield, Stevenage and Wolverhampton), supplying data for approximately 11,000 patients between 2004 and 2009 show that the proportion of patients presenting less than three months before initiation of RRT had fallen from 27.1% in 2004 to 17.0% in 2009, possibly as a result of the publication of national clinical guidelines or the quality and outcomes framework initiative (UK Renal Registry 2010). Udayaraj et al. (2011) attributed a falling trend and lower incidence of late referrals at an Oxford hospital unit between 2003 and 2008 to implementation of automated estimated glomerular filtration rate reporting and increased awareness of CKD in primary care.

In a similar vein, Farmer et al. (*in press*) assessed the impact of a computerised clinical decision support system (CDSS) to screen patients regularly having serum creatinine tests in primary care and found that six percent of the intervention group (n =98) were referred less than 90 days prior to commencing RRT as opposed to 25% of those not exposed to CDSS (n=353). Furthermore, those patients referred late were subdivided into those where the requirement for RRT was predictable (sustained GFR<30 mL/min/1.73m^2 or rapidly declining renal function) and those not predictable. In this group 2% (n=2) of those exposed to CDSS were referred less than 90 days prior to commencing RRT as opposed to 15% (n=52) of those not exposed to CDSS (Farmer et al. *in press*).

With respect to the demographic determinants of delayed referral ,the findings of the UK Renal Registry Report (2010) were in accordance with our own, although they reported that patients who presented late were significantly older than patients who presented more than 90 days before dialysis initiation [median age 67.0 *vs* 64.7 years, p < 0.0001].

Chronic Obstructive Pulmonary Disease (COPD)

No systematic reviews addressing late diagnosis and COPD were identified, but 12 primary studies examining this issue in the UK were found. After critical appraisal, 11 of these studies were included within our review.

There is considerable under-diagnosis of COPD with most people with COPD being undiagnosed. Some regional variation has been identified; late diagnosis seems to be particularly marked in urban centres, particularly London.

Diagnostic rates seem to be affected by GP and nurse supply. Spirometry and reversibility testing were not uniform across all practices and areas, and staff reported a lack of confidence and training in the use of spirometers and interpretation of results.

Under diagnosis was associated with hospital admissions for exacerbations.

There was no information about the cost implications of delay in the included primary studies.

Strategies to improve diagnosis included case finding and using specialist services for respiratory assessment.

Discussion of Recent Research

Avoiding crises is important for the patient as frequent exacerbations result in significantly faster decline (Donaldson et al. 2002) and a greater risk of mortality (Soler-Cataluna et al. 2005). Nevertheless, it has been reported elsewhere that exacerbations (with attendant hospitalisation and risk of death) are common even for those with moderate stages of the disease (Hurst et al. 2010).

Exacerbations, leading to hospitalisation, may also be avoided if patients with the condition are recognised and treated earlier (Celli et al. 2008, Seemungal et al.

1998). Crucially, recent research into drug treatments shows stronger effects in slowing the progression of the disease in its earlier phases (Jenkins et al. 2009).

Dementia

We found three systematic reviews examining late diagnosis and dementia (Bradford et al. 2009, Koch et al. 2010, Koch and Iliffe 2011).

Early dementia is harder to detect, with diagnostic sensitivity ranging from 0.09 to 0.41 in the milder stages, to a sensitivity range of 0.60 to 1.0 in severe cases.

Fear of a diagnosis affected patients and families, and made them reluctant to seek help. Fears centred round stigma, loss of independence and beliefs that nothing could be done. Primary care physicians shared the therapeutic nihilism of their patients and worried that a diagnosis would bring expectations of care that they could not fulfil.

Doctors acknowledged their difficulties in recognising the early stages of dementia and conducting tests in the short time available in a typical surgery consultation.

There was no information regarding either the outcomes or cost implications of late diagnosis of dementia in the included reviews.

Educational interventions increased healthcare practitioners' knowledge of dementia. Specifically, decision support software, practice based workshops and in- home assessment by nurses increased detection rates.

Depression

We found three reviews that examined late diagnosis in relation to depression (Cepiou et al. 2007, Das et al. 2006, Mitchell et al. 2011).

GPs and other non-psychiatric physicians were more likely to recognise people who did not have depression, than identify those who had the condition.

The evidence suggested that older people may be less likely to be diagnosed.

The milder stages of the disease were more difficult to recognise.

Discussion of Recent Research

Our findings echo the NICE guidelines which have cited studies suggesting that clinically significant depression (moderate to severe depressive illness) is detected by GPs at later consultations by virtue of the longitudinal patient-doctor relationship and it is the milder forms, which are more likely to recover spontaneously, that go undetected and untreated (National Institute for Health and Clinical Excellence, 2010).

Attempts to improve recognition and diagnosis of depression in primary care are reflected in the Quality and Outcomes Framework (QOF) indictors of the GP contract. Quality Indicator DEP 1 encourages the screening of patients by making a record of the percentage of patients with diabetes and/or heart disease for whom case finding for depression has been undertaken on one occasion during the

previous 15 months (NHS Evidence Clinical Knowledge Surveys, 2009). Recently, there has also been more focus on recognition by clinicians in acute hospital settings with an emphasis on co-morbidities, which (with respect to long-term conditions) most commonly include depression and dementia (personal communication via email 20.06.12, from Dr Hugh Griffiths, National Clinical Director for Mental Health).

The Improving Access to Psychological Therapies (IAPT) programme which supports the implementation of National Institute for Health and Clinical Excellence (NICE) guidelines for people suffering from depression and anxiety disorders anticipates that by 2015 a nationwide roll-out of psychological therapy services for adults will be completed, a stand-alone programme for children and young people will be initiated, and models of care for people with long-term physical conditions, medically unexplained symptoms and severe mental illness will be developed, with estimated savings of up to £272 million for the NHS and £700 million for the public sector (IAPT 2012).

Type I Diabetes

We found one systematic review relating to delayed diagnosis in type I diabetes (Usher-Smith et al. 2011). Usher-Smith and colleagues examined factors associated with the presence of diabetic ketoacidosis at diagnosis of new onset, previously undiagnosed type I diabetes in children and young adults.

Four studies within Usher-Smith et al. (2011) reported a substantial proportion (16-51%) of children experiencing delayed diagnosis (>24 hours for any reason).

Children aged five years or less, from an ethnic minority or having parents with lower educational or socio-economic status were more likely to present with diabetic ketoacidosis. One study showed that girls were more likely to experience a delayed diagnosis but did not have an increased risk of severe diabetic ketoacidosis.

A delay of more than 24 hours between initial presentation to a primary or secondary care provider and referral to a multidisciplinary diabetes team in the UK was associated with a four-fold increased risk of presenting with diabetic ketoacidosis.

One multicentre study included within Usher-Smith et al. (2011) showed that across Europe a delay of more than 24 hours between diagnosis and treatment was associated with a small increased risk of diabetic ketoacidosis in children.

Discussion of Recent Research

Further information regarding the determinants of delayed diagnosis and opportunities for improving the time to diagnosis of type I diabetes may be provided by as yet unpublished data from the Early Care Survey, conducted in the UK. The newly-established regional paediatric diabetes network system and the Association of Children's Diabetes Clinicians has been used to gather approximately 250 responses over a three month period in this national audit of the pre-hospital experience of parents of children newly diagnosed with diabetes. The influence of

factors including family structure, parents' educational level and socio-economic status upon delays to diagnosis (and the development of diabetic ketoacidosis) are being examined. Results from the audit will be available in late 2012 (Personal communication via email on 2nd May 2012 from Dr *Julie Edge,* Consultant in Paediatric Diabetes, *Oxford* Children's Hospital).

Epilepsy

Two systematic reviews were found relating to the misdiagnosis of epilepsy rather than delayed diagnosis of epilepsy (Chapman et al. 2011, Juarez-Garcia et al. 2006).

In addition, four primary studies provided very limited information about late diagnosis. However, experts recognize that it is a problem, related, partly, to late presentation. It is possible that over-diagnosis may present a more significant problem for this condition in adults.

In a UK national study, 27% of infants suffering from infantile spasms had a lead time to treatment of over two months.

Late treatment may contribute to developmental delay in children, and, in older patients, to an increased likelihood that the sufferer would not become seizure free after treatment.

One hospital managed to increase reduced the number of undetermined cases of epilepsy via case review and checks by independent neurologists.

Discussion of Recent Research

First seizure clinics have been established in several centres to ensure that patients receive the right advice and treatment. It is not considered clinically acceptable for patients to be put on routine waiting list for local neurologists after their first seizure as the opportunity for early intervention will be lost (personal communication from Dr Chris Clough, consultant neurologist, Kings College Hospital).

Recent NICE guidelines, published in 2012, on the diagnosis of epilepsy and training by the British Paediatric Neurology Association, may improve the situation for affected children and their families. An audit by the Royal College of Paediatrics and Child Health, due to report in September 2012, may throw further light on the problem of diagnosing epilepsy in children (personal communication from Dr Edward Wozniak, paediatrics advisor, Department of Health).

HIV

We found two systematic reviews relating to the delayed diagnosis of HIV (Chen et al. 2011, Deblonde et al. 2010).

Those declining a HIV test often perceived themselves to be at low-risk of infection. Conversely, those engaging in high-risk behaviours were more likely to avoid HIV testing due to fear of a positive diagnosis.

Fear of disclosure was a barrier to testing among African communities in the UK.

Uptake of testing was inhibited among migrants who thought that HIV status might have a bearing on the immigration process.

GPs were reluctant to discuss HIV testing with patients, even those from high-risk groups, and preferred to refer patients elsewhere for testing.

There was no information about the prevalence, outcome or cost implications of delayed diagnosis of HIV infection, and none of the primary studies within the included reviews examined interventions to reduce delayed diagnosis of HIV infection.

Discussion of Recent Research

Data from the Health Protection Agency suggests that the late diagnosis of HIV is substantial: of the 6,658 new HIV diagnoses made in 2010, 50% were late (with a CD4 cell count of <350/mm^3) and 28% very late (with a CD4 count <200 cells/mm^3) (Health Protection Agency, 2011).

A late (CD4 count <350/mm^3) or very late (CD4<200/mm^3) HIV diagnosis is associated with increased morbidity and mortality: a quarter of deaths among HIV positive individuals in the UK are among those diagnosed too late for effective treatment, and individuals starting antiretroviral therapy with a CD4 count below 350 cells/mm^3 have a significantly increased risk of contracting opportunistic diseases (Health Protection Agency, 2011). Furthermore, undiagnosed individuals have been estimated to have a rate of onward transmission three times higher than those who are diagnosed with HIV infection, and be more than twice as likely to have unprotected sex (Marks et al. 2006).

Recent UK primary research has demonstrated that the annual treatment cost for HIV infected individuals decreased as CD4 count increased, with the biggest differences observed between starting highly active anti-retroviral treatment regimens (HAART) with a CD4 count ≤200 cells/mm^3 compared with a CD4 count >200 cells/mm^3 (Beck et al. 2011a). Beck and colleagues concluded that while starting patients on a first-line HAART regimen at CD4 counts ≤350 cell/mm^3 would increase the number of patients receiving HAART and initially increase the population costs of providing HIV services, earlier treatment on cost-effective regimens would maintain patients in better health and result in reduced use of health and social services (thereby generating fewer treatment and care costs and enabling people living with HIV to remain socially and economically active members of society). Nevertheless, Beck et al. (2011b) note that 25% of HIV positive individuals accessing services continue to present with a CD4 count ≤200 cells/mm3, which highlights the need to investigate the cost-effectiveness of testing and early treatment programs for key populations in the UK.

The National Institute for Health and Clinical Excellence has produced a costing model which estimates that a shift of 1% of patients being diagnosed at an earlier stage of disease effects a reduction in treatment costs and creates savings: approximately £212,000 a year for men who have sex with men and £265,000 a

year for black Africans in England. The cumulative effect of onward transmissions avoided means that over time savings would increase and become greater (NICE, 2011).

Eight Department of Health funded projects conducted in high prevalence areas in the UK between 2009 and 2010 resulted in more than 10000 HIV tests being performed and appeared to be effective in detecting new cases: together they generated a total of 50 newly diagnosed individuals giving an overall positivity of five per 1000 tests. The estimated annual cost of expanding testing into general medical services nationally in areas of high prevalence with coverage of 75% would be £1.3 million: the cost for an average high prevalence PCT would be £19,000 per 100,000 people (Health Protection Agency, 2010).

Finally, since the introduction of the universal offer of an HIV test as part of routine antenatal care in 1999, uptake of HIV testing among women in antenatal care has reached 95% nationally. The proportion of women who remain undiagnosed after delivery fell from 27% in 2000 to 12% in 2009 and the estimated proportion of newborns at risk of HIV infection who become infected fell from 8% to 2% between 2000 and 2008 (Health Protection Agency, 2010).

Myocardial Infarction

We found six systematic reviews that examined ST-segment elevated myocardial infarction (STEMI) (Brainard et al. 2005, Hewitt et al. 2004, Dubayova et al. 2010, Morrison et al. 2006, Boersma et al. 2006, De Luca et al. 2008). Much of the information in the reviews is out of date as medical practice in this field has moved on since they were published.

Patient delay is the most difficult area to tackle and evidence from public awareness campaigns is weak, suggesting that the increase in the use of emergency services is not offset by gains in earlier diagnosis.

Pre-hospital ECG, administered by paramedics, decreases the time to treatment.

Primary percutaneous coronary intervention is the treatment of choice despite the need to transfer some patients to a specialist centre.

There is no information on prevalence, outcomes or costs in the reviews.

Discussion of Recent Research

Recent UK research by Quinn et al. (forthcoming) on a large dataset of patients from the MINAP (Myocardial Ischaemia National Audit Project) registry found that pre hospital ECG enabled patients to receive treatment within the recommended time ('call to balloon' time $\leq$ 90 mins (27.88% vs 21.42%, OR 0.73, 95% CI 0.65-0.81) for PPCI, and 'door to needle' time $\leq$ 30 mins (90.61% vs 83.68%, OR 0.54, 95% CI 0.47-0.62) for those receiving fibrinolytic therapy in hospital).This, in turn, affected mortality, with lower hospital (4.0% vs 4.7%, OR 0.91, 95% CI 0.86-0.95) and 30 day (7.4% vs 8.2%, OR 0.95, 95% CI 0.91-0.99) mortality for STEMI patients who received reperfusion treatment. Pre hospital ECG use increased from 48% to

68% over the period of the study (January 2005 to December 2009), but overall only 50.3% of emergency patients received pre-hospital ECG.

In 2002 few UK centres offered PPCI, but evidence, from trials and observational studies (Huynh et al. 2009), showed that the procedure offered greater benefits in terms of survival and complications than thrombolysis treatment. The National Infarct Angioplasty Project (NIAP) was established to collect and analyse data from seven PPCI pilots from April 2005 to March 2006. In 2008, they concluded their study and reported that PPCI could be delivered within acceptable treatment times. Of those patients admitted directly to a catheter laboratory in a PPCI centre, 98% achieved a 'door to balloon' (DTB) time of less than 90 minutes (NIAP 2008).

Since 1999, MINAP has collected clinical audit data from a network of hospitals on the care of patients with heart attack. In 2011, it reported an increase of centres offering PPCI over the last 10 years from 86 in England and 2 in Wales to 133 and 8 respectively. Ninety percent of patients in England were treated with PPCI within 90 minutes of arriving in hospital, the recommended time interval. For PPCI, a greater percentage of patients were treated within the recommended time, i.e. 150 minutes from calling for professional help, if they were taken directly to a heart attack centre – 88% in England, 76% in Wales, 89% in Belfast (MINAP 2011).

Since the publication of the National Service Framework for Coronary Heart Disease in 2000 (Dept of Health 2000), NICE has produced guidelines for the management of nSTEMI (National Clinical Guidelines Centre 2009) and guidelines for STEMI will be published soon, based on more recent primary studies. Data from a recent study looking at delays to reperfusion across four regions of the world show that Europe (including data from the UK) has the shortest times to PPCI and fibrinolysis (Spencer et al. 2010).

Psychosis

We found seven systematic reviews relating to delayed diagnosis for psychosis (Anderson et al. 2010, Bird et al. 2010, Farooq et al. 2009, Lloyd-Evans et al. 2010, Marshall et al. 2006, Marshall and Rathbone 2011, Perkins et al. 2005).

The duration of untreated psychosis, i.e. the time interval between symptom initiation and diagnosis and/or treatment, was found to have a median of 21.6 weeks, with a range of four to 68 weeks.

Longer duration of untreated psychosis (DUP) is associated with greater severity of positive symptoms after treatment, greater severity of global symptoms after treatment, poorer social functioning, more likely relapse and lower rates of remission.

We found no information about cost implications in the included reviews.

The results of studies reporting on the impact of multi-focus awareness campaigns on reducing DUP were mixed and conflicting.

Specialised teams with lower case loads, drawing on a variety of approaches including medication, psychotherapy and family support, may be the most effective tactic in improving outcomes of first episode psychosis. However, larger trials are needed to confirm this.

Results from small scale trials, which have not been replicated, suggest that E-EPA oil, the anti-psychotic amisulpride, and a combination of anti-psychotics and CBT are strategies that warrant further investigation for the prevention of transition to psychosis.

Discussion of Recent Research

The reviews do not tell us where in the diagnostic process delay is most likely to occur, but primary research conducted by Brunet et al. (2007) in the UK indicated that the median delay within secondary services was over seven times the delay in the referral pathway, with a mean delay in mental health services accounting for 35% of overall DUP. Data from Anderson et al. (2010) suggests that those from ethnic minorities are more likely to experience a pathway into care that involves emergency services or an element of compulsion. Nevertheless, a UK study (Morgan et al. 2006) found no evidence that African-Caribbean or Black African patients experienced longer periods of untreated psychosis than White British patients prior to first contact with services.

There is good evidence that early intervention services (EIS) improve outcomes for those with first episode psychosis, but larger trials may be needed. Pertinent evidence may be supplied by a full-scale RCT (Recovery After an Initial Schizophrenia Episode - RAISE), comparing two different ways of providing early treatment to people experiencing the early stages of schizophrenic disorders. As part of the RAISE trial, patients are currently being recruited at 34 study locations throughout the US to evaluate EIS including personalized medication treatment, individual resiliency training, supportive services, family psycho-education and education/ employment assistance (National Institute for Mental Health, *ongoing*).

Maintaining gains is a critical issue within the treatment of psychosis and few trials showed gains preserved beyond the treatment period - it may be that EIS are only effective while interventions are active (Birchwood and Fiorillo 2000). Research currently being conducted in the UK, the SuperEDEN (Sustaining Positive Engagement and Recovery) project, is following up a cohort of patients to examine outcomes after being discharged from services (UK Clinical Research Network, 2012).

Stroke

We found four systematic reviews focusing on stroke (Jones et al. 2010, Kwan et al. 2004, Lecouturier et al. 2010a/b)

A lack of awareness of the warning signs of stroke or transient ischaemic attacks (TIA) leads to delays in seeking help by sufferers or witnesses. This lack of knowledge is seen at the same levels for stroke patients or those at risk of stroke as the general public.

Inappropriate action, as well as lack of recognition of symptoms, contributes to delays to hospital arrival, with the majority of patients phoning their GP rather than an ambulance.

Public education campaigns were successful in increasing the knowledge of symptoms, but not in improving the awareness of the need to access the emergency services.

Multi component interventions showed some promise in reducing the time from onset to the administration of thrombolysis therapy.

There was no information about outcomes and the cost implications of late diagnosis.

Discussion of Recent Research

Recently, the Department of Health instigated a major 3 year communications campaign, *the FAST test:* Facial weakness, Arm weakness, Speech difficulties and Time to act fast, which commenced in February 2009 with the objective of enabling members of the public to recognise and identify the main symptoms of stroke and know that it needs to be treated as an emergency. The campaign used mass media including television, print, radio and the internet (Department of Health, 2009). An evaluation of the FAST campaign suggested that it performed well in terms of spontaneous and prompted recognition of the symptoms of stroke but that knowledge was highest following the second of five waves of the campaign, when spend was highest (TNS BMRB, 2010). Following the most recent advertising campaign in March 12, an independent tracking survey among over 1800 adults, carried out by TNS BMRB, showed that the campaign was successful in increasing knowledge of stroke symptoms (any symptom:98%) and in improving awareness of the need to access services to the highest level seen so far at 74%. Higher scores were achieved by those aware of the FAST campaign and improvements were seen among key BME group also, (personal communication from Karen Pinder, Health Protection and Older People's Marketing Manager, Department of Health). An evaluation of stroke awareness campaigns conducted in England, Australia and Canada using pre- and post-campaign surveys found the greatest improvement in stroke awareness was created by the multifaceted FAST campaign, which had the greatest budget and reach (Trobbiani et al. *in press*).

Tuberculosis (Findings from systematic reviews)

Four systematic reviews examined late diagnosis and tuberculosis (Courtwright and Turner 2010, Liu et al. 2008, Sreeramareddy et al. 2009, Storla et al. 2008).

Statistically, there was no difference in time delays in low or high endemic countries, or low, middle, or high income countries.

The type of health care site and/or health practitioner that is initially accessed by patients seems to impact on the speed of diagnosis. Poverty, rural residence, being a woman, low awareness of tuberculosis and older age are associated with a greater risk of late diagnosis.

There was no information about the outcomes or cost implications of late diagnosis of tuberculosis within the included reviews.

There may be some merit in reminder systems to encourage return for results of tests, but more robust trials are needed.

Tuberculosis (Findings from UK primary studies)

Data on the prevalence of late diagnosis in the UK were limited. One study found that 50% of a small sample of patients prescribed antibiotics prior to confirmation of TB diagnosis experienced treatment delay. Another small study found that, of 62 patients with TB, only 4 out of 38 in-patients had been diagnosed prior to admission.

Being female, older, of white ethnicity or socio-economically deprived was associated with delays in the initiation of treatment.

Among White and UK born patients, shorter intervals were experienced by the most deprived. Recent migrants were less likely to experience delays, as were patients with pulmonary rather than extra-pulmonary disease.

Patient denial, delayed presentation and non-compliance were identified as barriers to diagnosis. Among GPs, a low index of suspicion, a lack of knowledge and sub-optimal clinical-patient communication were identified as barriers to diagnosis.

One small study investigating the utilization of healthcare resources by patients with TB demonstrated a very high rate of in-patient care, judged to be a consequence of the emergency admission of acutely ill, previously undiagnosed cases.

Both screening and case management support components of the London 'Find and Treat' outreach service for hard to reach patients with TB were found to be cost effective.

An educational programme resulted in the improved identification of active and latent tuberculosis, a higher percentage of new registrations screened for TB, and higher median numbers of tuberculin skin tests being carried out in intervention practices compared with controls.

Discussion

Where is late diagnosis of most concern?

There are four conditions were late diagnosis is of most concern: COPD, Dementia, HIV and Type 1 Diabetes.

COPD has a particularly high prevalence of late diagnosis, with an estimated 80% of cases remaining undiagnosed. Many of these cases are likely to be patients in the milder stages of the disease. Crucially, recent research into drug treatments shows stronger effects in slowing the progression of the disease in its earlier phases (Jenkins et al. 2009). Under-diagnosis was associated with costly hospital admissions for exacerbations of the condition.

Early dementia is harder to detect, with diagnostic sensitivity ranging from 0.09 to 0.41 in the milder stages, to a sensitivity range of 0.60 to 1.0 in severe cases, with doctors acknowledging their difficulties in distinguishing between dementia and 'normal ageing'. There was some ambivalence about diagnosing patients early because both doctors and families of patients could not see therapeutic value in doing so.

There was evidence to suggest that a substantial proportion (16–51%) of children experience delayed diagnosis in type I diabetes (>24 hours for any reason).

Those engaging in high-risk behaviours were more likely to avoid HIV testing due to fear of a positive diagnosis, which has worrying implications with regard to onward transmission. Data from the Health Protection Agency indicates that 50% of new diagnoses are late in the UK.

There were some conditions where the lateness of the diagnosis had a considerable impact, such as chronic kidney disease and psychosis, leading to high morbidity and mortality, and less likelihood of remission or positive response to treatment. In these two cases, interventions such as early intervention services (psychosis) and decision support software for primary care staff (CKD) have improved the situation.

For myocardial infarction (STEMI) and stroke, the treatment available has improved considerably over the last decade and the health system has been re-organised to deliver the best care. However, patient delay remains an intractable problem and the mass media public awareness campaigns have not been as successful as hoped.

Who is most likely to experience late diagnosis?

Broadly, late diagnosis affects vulnerable groups such as older people or those living in poverty.

Age was identified as a barrier to early diagnosis in the included research. Older age was distinguished as a determinant of delay in the diagnosis of depression, tuberculosis and COPD. In contrast, younger age was found to be a barrier to diagnosis in those suffering from type 1 diabetes. Delayed diagnosis for older people might be a consequence of the increased presence of confounding co-morbidities in this age group. Alternatively, delayed diagnosis for older patients may be a result of beliefs held by doctors and patients that nothing can be done to halt progression (as was the case for dementia patients), that deterioration in health is to be expected as age increases, or simply of ageism.

Females were more likely to experience a delayed diagnosis of dementia, type I diabetes or tuberculosis.

A lower socio-economic status was implicated in delayed diagnosis both for type I diabetes and tuberculosis. Delayed diagnosis among less affluent populations may occur due to access difficulties or that fact that generally, less prosperous people demonstrate poorer health and are more likely to suffer from the co-morbidities which contribute to missed diagnoses. Low education levels were associated with delay in dementia, tuberculosis and type I diabetes.

Belonging to an ethnicity minority was associated with presenting with diabetic ketoacidosis at diagnosis of type I diabetes in children and young adults. White patients were more likely to experience delays in the treatment of tuberculosis than ethnic minorities. Language barriers were mentioned by doctors when discussing communication problems with patients suffering from dementia.

Categorising delay

We found very little research examining administrative, organisational or procedural (system) determinants of diagnostic delay. System barriers to diagnosis require further investigation. Among this type of determinant, resource constraints and access issues were more frequently discussed than organisational/management issues. This may simply be a reflection of the fact that these factors are easier to record and investigate.

The Hansen model (Hansen et al. 2008) served as a useful starting point for categorising delay in order to create our systematic map. However, types of delay occurring for one condition may be specific to that condition, e.g. where symptoms are slow to appear. Any one model is bound to have limitations when trying to describe delays for the late diagnosis literature across all conditions. Ultimately, universal indicators for delays to diagnosis may be an unattainable goal due the disease-specific nature of delays within a particular condition.

It may be more useful to conceive of delays to diagnosis in terms of the length of intervals within the diagnostic process and factors impacting upon, or prolonging these intervals. However, with the exception of reviews which focused upon delays occurring in the diagnosis of tuberculosis (Sreeramareddy et al.2009, Storla et al. 2005) and myocardial infarction (Boersma et al. 2006, De Luca 2008), the included reviews did not present any information with regard to specific time intervals within the diagnostic process. It may be that this practice is not sufficiently established to be described in systematic reviews as yet.

Patient delay

Patient delay was identified as barriers to prompt diagnosis and treatment for a number of conditions including chronic kidney disease, dementia, HIV, stroke, myocardial infarction, epilepsy and tuberculosis. Symptom misinterpretation and lack of knowledge were implicated in delayed presentation. In the case of epilepsy, the patient may be unaware of their condition until an attack is witnessed by another. Fear often appeared to influence patients' help-seeking behaviour.

Three of the four reviews concerning stroke concentrated on studies that described patient delay and its relationship with knowledge of the symptoms and warning signs of stroke. Lack of knowledge of the warning signs of a stroke or a TIA, as well as lack of action needed when a stroke is suspected, were found to be major determinants of delay. There was a similar finding for patients with STEMI.

Patient fear, denial, non-compliance with investigations and symptom misinterpretation were identified as barrier to prompt diagnosis and treatment of tuberculosis. Similarly, patients appeared to delay going to the doctor for fear of

the stigma of mental illness associated with a diagnosis of dementia, and the subsequent loss of independence. Patients and their families may not recognise early symptoms of dementia, or may have got used to compensating for their relatives' cognitive deterioration. There was a perception that there were few treatment options for dementia, so early diagnosis was not desirable. Low risk perception, fear of a positive diagnosis and fear of disclosure were all identified as barriers to HIV testing. Those declining a HIV test often perceived themselves to be at low-risk of infection. Conversely, those engaging in high-risk behaviours were more likely to avoid testing as a result of fear of a positive diagnosis. Fear of disclosure was a particular concern among African communities in the UK. Uptake of testing was inhibited among migrants who feared that HIV status might have a bearing on the immigration process.

It may be difficult to address patient delay, particularly where delays to help-seeking behaviour are influenced by fear (of disease or stigma). Where delay is caused by lack of knowledge, mass media campaigns can be employed to reduce symptom misinterpretation or delay in seeking appropriate help. However, such campaigns can be extremely costly and this review has not identified robust evidence of success. For stroke, public education campaigns were successful in increasing the knowledge of symptoms, but not in improving the awareness of the need to access the emergency services. For psychosis, the results of studies reporting on the impact of multi-focus awareness campaigns on reducing treatment delay were mixed and conflicting. With regard to myocardial infarction, the increased use of emergency services from public awareness campaigns has to be of concern as it places extra burdens on the health service and does not appear to result in significant gains to early diagnosis.

Doctor delay

Inadequate knowledge and training were identified as barriers to prompt diagnosis and treatment for chronic kidney disease, COPD, dementia and tuberculosis.

Diagnosing dementia in its early stages was judged to be difficult as symptoms were fluctuating and non-specific. Primary care providers wished to have more education about what constitutes ‘normal ageing’ so they were able to make accurate diagnoses. They expressed discomfort at using diagnostic tests and wanted greater support and input from specialist colleagues in secondary care. Lack of training in the use of spirometry contributed to the lack of confidence in using the equipment for the diagnosis of COPD. Spirometry was performed more often by those who were confident of interpreting the results. General practitioners' low index of suspicion, lack of knowledge and sub-optimal communication with patients were identified as barriers to the prompt diagnosis and treatment of tuberculosis. The improvement in identification of patients with tuberculosis, produced by a campaign to educate primary healthcare practitioners, suggests that it is possible to remedy deficits in clinical knowledge, although it may be difficult to replicate this success for other diseases or conditions in which a low index of suspicion is not a critical factor.

Communication difficulties were identified as barriers to diagnosis for chronic kidney disease, dementia, HIV and tuberculosis. Difficulties in disclosing and explaining a diagnosis of dementia were reported. Anxiety and reticence were also described among GPs reluctant to discuss HIV testing with patients (even in high-risk groups), which resulted in delays due to onward referral. Patients suggested that GPs failed to adequately communicate the value of HIV testing. Finally, therapeutic nihilism was also exhibited by doctors, who were reluctant to initiate investigations as they were uncertain about what support might be available to dementia patients or what they might offer in support by way of treatment or services. In appears therefore, that factors over and above constraints to consultation time are impacting upon optimal communication between patients and clinicians.

System delay

The most frequently identified system determinants of delays to diagnosis were restricted access, insufficient consultation time and resources constraints. Access issues, in terms of geographical location or knowledge of availability of services, were described for chronic kidney disease, HIV and tuberculosis. GP workload and suboptimal continuity of care were identified as barriers to the prompt diagnosis and treatment of TB. Insufficient consultation time was also described as impeding diagnosis of dementia: the time of a typical visit to a doctor's surgery did not allow for the completion of diagnostic tests. Resource constraints also hindered the early detection of dementia. Doctors also felt discouraged by the low reimbursement for dementia care. There was evidence to suggest that the supply of primary care affects diagnostic rates for COPD. Key informants in the field of HIV and working with African communities in the UK noted that financial and human resources were often lacking in order to target African communities in the UK. Economic evaluations elucidating the cost-effectiveness of earlier diagnosis and treatment, should serve to identify where to direct resources in order to make best use of limited budgets.

Interventions

Early diagnosis of some conditions may be difficult to improve upon due to non-specific presentation (e.g. dementia) or due to aggressive onset of disease (e.g. type 1 diabetes). Nonetheless, having established whether or not those with a particular condition are likely to experience delayed diagnosis, and the effect that delayed diagnosis will have upon mortality and morbidity, the question immediately arises as to what can be done to promote early diagnosis and prompt treatment. Treatment delay may be considered equivalent to late intervention. However, an unmanageable quantity of literature was generated using terms to capture the concept of "early/late intervention" during the early stages of this review. Thus, literature was sought and examined only where "early/late intervention" and "treatment delay" occurred alongside diagnosis terminology. Indeed, much of the literature examining early intervention is focused on the timing of treatment in relation to prognostic or clinical factors rather than undue or avoidable delay. Nevertheless, we must acknowledge that we may have failed to

locate a proportion of the literature examining early intervention. Future research may help to identify this potential source of evidence.

For dementia, there was some evidence that doctor education improved the detection of the condition. However, the trials reviewed were not large and so could not present robust findings, and only one was conducted in the UK. An UK educational programme intended for primary care health professionals, resulted in improved identification of active and latent tuberculosis and a higher percentage of new registrations screened for TB in those practices exposed to the intervention.

Multi-component interventions showed some promise in reducing the time from onset to the administration of thrombolysis therapy for those suffering a stroke. However, public education campaigns were successful in increasing the knowledge of stroke symptoms, but not in improving the awareness of the need to access the emergency services. While the bulk of the literature focused upon delays within primary healthcare, we found relatively few studies examining mass media/patient education campaigns. This may be due to the expensive nature of such campaigns, or concerns about their efficacy or the longevity of their impact.

Specialised early intervention teams with lower case loads, drawing on a variety of approaches including medication, psychotherapy and family support, may be the most effective tactic in improving outcomes of first episode psychosis. However, the results with regard to interventions to reduce the duration of untreated psychosis were mixed and conflicting.

There was evidence to suggest that reminder systems produced shorter delays in tuberculosis diagnosis, but more substantive trials are required. Similarly, case finding strategies, targeted at high-risk groups may prove useful for identifying individuals with COPD and tuberculosis.

Medical advances in cardiology have been utilized by the health system to improve emergency care for patients suffering a heart attack. In the last decade, the re-organisation of services so that a majority of patients have rapid access to catheter laboratories and primary angioplasty, has resulted in lower mortality and morbidity for those patients who present in less than 6 hours from the onset of symptoms.

Costs

There was very little material about the cost implications of delayed diagnosis, but this may reflect a general dearth of economic data in the biomedical literature as a whole, and in systematic reviews in particular. Although authors of primary studies often report costs or cost-effectiveness, it is rarely the case that they provide data in a format which can be used within systematic reviews. Therefore, the presence of reliable cost-effectiveness data within reviews of reviews, including this one, is scant. Both Brown and Grimes (1995) and Dierick van Daele et al. (2008) have discussed the challenges in obtaining cost-effectiveness data for systematic review.

Economic evaluations need to weigh the initial increase in demand upon services that results from earlier diagnosis against savings attributable to avoiding the treatment of advanced disease, and the avoidance of losses due to individuals

remaining socially and economically active. Where diseases are communicable, savings accrued from reduced transmission may be substantial – as has been suggested for HIV.

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The **Evidence for Policy and Practice Information and Co-ordinating Centre** (EPPI-Centre) is part of the Social Science Research Unit (SSRU), Institute of Education, University of London.

The EPPI-Centre was established in 1993 to address the need for a systematic approach to the organisation and review of evidence-based work on social interventions. The work and publications of the Centre engage health and education policy makers, practitioners and service users in discussions about how researchers can make their work more relevant and how to use research findings.

Founded in 1990, the Social Science Research Unit (SSRU) is based at the Institute of Education, University of London. Our mission is to engage in and otherwise promote rigorous, ethical and participative social research as well as to support evidence-informed public policy and practice across a range of domains including education, health and welfare, guided by a concern for human rights, social justice and the development of human potential.

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