CURRENT TOPIC

Screening in infancy

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Screening is an attractive approach to preventive medicine, but it can damage health as well as improve it. In 1968, Wilson and Jungner set out 10 criteria by which new screening programmes could be assessed.[1] It is difficult for a programme to fulfil all the criteria but failure in just one can be the downfall of an otherwise excellent project. The Wilson and Jungner criteria have stood the test of time[2] but we will suggest some minor changes and consider their relevance to paediatric practice, with special reference to a proposed screening programme for extrahepatic biliary atresia (EHBA) and other liver diseases of infancy (table 1).[3]

Criterion 1 – the condition must be an important public health problem

'Important' in this context cannot be judged by frequency alone. As children become healthier, rare diseases assume increasing significance. Phenylketonuria for example is rare, but the phenylketonuria programme is cost effective and fulfils screening criteria very well. Nevertheless, there are rarely sufficient data to permit a totally objective analysis and value judgments will always have to be made, taking into account the nature of the disease process, the distress and suffering caused, and the emotional impact of these on the family and society.

Criterion 2 – an effective treatment must be available

This may not be an essential criterion in paediatric practice (see criterion 8).

Criterion 3 – facilities for diagnosis and treatment should be available

Conditions such as EHBA should usually be managed in tertiary centres. Delays in referral for definitive investigation and treatment are sometimes due to professional failure, at primary or secondary care level, to recognise the nature of the problem[4] – for instance, EHBA may be misdiagnosed as breast milk jaundice. A less forgivable cause of delay is the desire to investigate an 'interesting case' oneself. Screening programmes cannot address

Table 1 Wilson and Jungner's criteria[1] for screening programmes and comments on proposed screening programme for liver disease and EHBA

	Wilson and Jungner's criteria (proposed modifications in italics)	*Comments on proposed screening programme for liver disease and EHBA*
1.	The condition to be sought should be an important public health problem *as judged by the potential for health gain achievable by early diagnosis.*	Incidence is same order of magnitude as phenylketonuria or hypothyroidism; importance in terms of screening is the benefit of early treatment.
2.	There should be an accepted treatment *or other beneficial intervention* for patients with recognised *or occult* disease.	Effective treatment available.
3.	Facilities for diagnosis and treatment should be available *and shown to be working effectively for classic cases of the condition in question.*	Delays in referral of classic cases are a significant cause of late treatment but are not due to lack of facilities.
4.	There should be a latent or early symptomatic stage *and the extent to which this can be recognised by parents and professionals should be known.*	Existence of the latent stage not in doubt but difficulty in recognition – see criteria 5 and 6.
5.	There should be a suitable test or examination. It should be simple; valid for the condition in question; reasonably priced; repeatable in different trials or circumstances; sensitive; specific. The test should be acceptable to *the majority* of the population.	The main problem – see table 2.
6.	The natural history of the condition *and of conditions which may mimic* it should be understood.	The natural history of neonatal jaundice and breast milk jaundice is not fully documented.
7.	There should be an agreed definition of what is meant by a case of the target disorder; *also an agreement as to (i) which other conditions are likely to be detected by the screening programme, (ii) whether their detection will be an advantage or a disadvantage.*	There is an agreed definition of EHBA and the detection of other liver diseases will be beneficial.
8.	Treatment at the early, latent, or presymptomatic phase should favourably influence prognosis, *or improve outcome for the family as a whole.*	There is no doubt that early recognition of EHBA and other liver disorders improves prognosis.
9.	The cost of screening should be economically balanced in relation to expenditure on the care and treatment of persons with the disorder and to medical care as a whole.	True costs of screening for EHBA not known but are probably higher than estimated by Mowat *et al.*[3]
10.	Case finding *may need to be* a continuous process and not a once and for all project, *but there should be explicit justification for repeated screening procedures or stages.*	The need for repeated screening and continuous vigilance will need to be assessed in field trials of a screening programme.

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Table 2 Terms used in evaluation of screening tests

	Diagnostic test		
Screening test result	*Positive*	*Negative*	*Totals*
Positive	a	b	a+b
Negative	c	d	c+d
Totals	a+c	b+d	a+b+c+d

Sensitivity $= \frac{a}{a+c}$

(that is, the proportion of all true cases found by the screening test or programme).

Specificity $= \frac{d}{b+d}$

(that is, the proportion of all healthy people correctly identified by the test or programme).

Positive predictive value $= \frac{a}{a+b}$

(that is, the proportion of all positive screening tests which result in confirmation of a true case).

NB: The first two of these parameters are properties of the test itself, but the third is affected by the frequency of the condition in the population; as a condition becomes less common, the ratio of false positive to true positive cases increases.

these problems and are unlikely to improve the situation unless the referral and management of classic cases are optimal. Better collaboration between secondary and tertiary care teams, a programme of awareness raising, and continuous monitoring of age of referral and avoidable delays, might together do more to achieve earlier diagnosis than a screening programme.

When introducing a new screening programme, the whole diagnostic pathway from failed screening test to definitive management should be planned as an integrated process. The inevitable anxiety felt by parents of a child who has screened positive[5] can be minimised by provision of well presented information about the test and its significance, prompt referral, and speedy investigation and interpretation of results (P Gibson, D M B Hall, unpublished). From the parental perspective, 'prompt' means days, not weeks and certainly not months. For some parents with high background anxiety levels, a positive screening test can cause long term distress, even if it turns out to be a false alarm.[6]

Many screening programmes have foundered because no one person is in charge of the whole exercise, including audit and quality assurance. There must be a director of each programme, who can take a broad view of the process from first patient contact to tertiary specialist, if the benefits are to be realised and the hazards of screening kept to a minimum. It is unethical to embark on a screening programme unless resources are available to set and maintain high standards.[7]

Criterion 4 – there should be a latent or early symptomatic phase

The word 'latent' may mean that there really are no symptoms or signs, but more often the features are potentially detectable by parents as well as professionals, as is the case with jaundice. A screening programme might be justified if the symptom or sign in question is substantially more likely to be identified and acted upon by a trained screener than by the parent. Before it is assumed that this is the case, it may be important to test the benefits (and hazards) of teaching parents how to identify possible abnormality and obtain relevant professional advice.

Criterion 5 – there should be a suitable test

Screening tests are often portrayed as being simple, cheap, and convenient. They seldom are.[8] A test that provides the clinician with useful information about a sick child does not necessarily perform equally well as a screening test in apparently healthy subjects. In the case of EHBA and other liver diseases, there is no single diagnostic test and a series of specialised investigations is needed. In this situation, it is difficult to design a simple screening test.

It is the purpose for which the test is being used, not the nature of the procedure, which decides whether or not it should be regarded as a screening test. Holland and Stewart emphasised that 'asking individuals simple questions ... identifies individuals who are at risk and can be legitimately considered under the definition of screening'.[9] We do not know whether giving parents information about prolonged jaundice, pale stools, and dark urine might facilitate earlier diagnosis of EHBA, but it is quite feasible to measure the sensitivity, specificity, and positive predictive value (defined in table 2) of information given in the form 'Have you observed X? If so, do Y'. These parameters can be assessed not only for each individual question, observation or test, but also for a screening or diagnostic algorithm.

Could liver disease in infancy be identified by the presence of persistent jaundice? Jaundice is found in 15% of babies at 2 weeks, 2·6% at 4 weeks, and 0·6% at 6 weeks (D A Kelly, A Stanton, personal communication). Second line tests have therefore been proposed to reduce the number of referrals. These include urine or blood tests for conjugated bilirubin and the observation (by parent or health visitor) of pale stools and dark urine. Collecting blood or urine presents obvious practical problems. There are technical difficulties with the estimation of conjugated bilirubin and haemolysis in the blood sample may invalidate the results. Little information is available about normal variations in stool or urine colour, but these deserve further study.[10] Thus, the sensitivity, specificity, and positive predictive value (table 2) of the first stage of screening, the detection of jaundice, can be estimated, but there are insufficient data to estimate these parameters for the complete screening algorithm.

Not only the test, but the whole concept of screening must be culturally acceptable. A physical examination or a urine specimen may be permitted more readily by parents than a heel prick or venepuncture. No screening programme, however, will be acceptable to 100% of the population. For example, 3% of parents rejected an offer of neonatal hearing

screening.[11] This may reflect reluctance to submit the newborn infant to any medical procedure; or it may be a form of self protection in the face of other anxieties or multiple stress factors[12] – the parent feels that they just could not cope with bad news about their baby's health.

Criterion 6 – the natural history should be understood

New screening programmes sometimes reveal that the natural history of the condition is less well understood than was previously imagined (as happened with screening for adolescent scoliosis). The identification and management of mild variants of normal and benign conditions may consume more resources than the target condition itself (see criterion 9).

Criterion 7 – there should be an agreed case definition

Sometimes, a 'case' can be defined unequivocally by a clinical syndrome or a single laboratory test. At the other end of the scale, there are conditions such as dyslexia whose very existence is controversial. In between, there are conditions like EHBA, which is a recognised entity but cannot easily be characterised by any preoperative diagnostic test. Screening therefore involves use of a proxy measure such as jaundice. Inevitably, this will identify not only the target disorder but also a number of 'byproducts'. In the programme proposed for EHBA, the early identification of other liver diseases would be facilitated (a bonus), but many cases of breast milk jaundice would be found[13]; this would worry mothers and might lead them to discontinue breast feeding unless considerable time was devoted to explanation and support.

Criterion 8 – early treatment should improve outcome

Many screening programmes have been launched in the confident belief that early intervention will improve outcome. In some instances, for example in congenital sensorineural deafness, it may never be possible to determine whether this is so. In others, such as Duchenne muscular dystrophy, the outcome is not improved but parents can plan for the future and avoid the birth of a second affected child.

Why does early diagnosis of serious disease seem so important to parents even when it makes little or no difference to outcome? Parents will always speculate about what might have happened if treatment had been started earlier. Avoidable delays in diagnosis and referral feed the natural sense of anger and betrayal felt by the parents of a sick child. Parents of disabled children say that they want to know about the child's problems as soon as possible. It seems that the longer the parents' shared life with a child they believe to be normal, the more devastating is the discovery of a serious illness or disorder. If they have received good care from the first suspicion through to tertiary referral, their memories of the whole process, though still painful, will be less embittered.

Criterion 9 – cost of screening should be economically balanced

The cost can be stated in terms of the total programme cost, the cost per child screened, or the cost per case detected. The true costs are usually underestimated and include test materials or reagents; written information about the condition (for example in the personal child health record); professional time spent in explaining the test and obtaining consent, performing and interpreting the test, assessing and reassuring screen failures at the specialist clinic, monitoring and auditing the programme; time to answer further questions and queries; training staff; insurance against litigation resulting from badly performed tests or failure to test the whole population. Some authorities include the parents' time and travel to hospital for investigation[14] and the cost of psychological distress associated with false positive screening tests.

Programme costs are not directly proportional to the volume and duration of work generated by the new test.[15] For example, a procedure that can be completed in one or two minutes might be absorbed into existing work routines without appreciable cost to other activity, but one that takes 10 or 15 minutes (such as obtaining and testing a urine specimen) might require either an increase in staff or reduction in some other service. Similarly, a screening procedure for EHBA might be affordable if it could be incorporated into the first visit by the health visitor, but the cost would escalate if a separate visit were needed specifically for that purpose, for instance at 21 or 28 days.

The cost per case detected is calculated by dividing the programme cost by the number of cases actually discovered *by the screening programme*, not by the total number of cases in the population being screened. The benefits of screening, however, may not necessarily be realised as a direct result of the screening test itself. Some cases of a condition like EHBA will be ascertained by other means, and this number may well increase as a result of the raised awareness generated by a screening programme.

How much are we prepared to pay to ensure that all cases of EHBA are diagnosed by the age of 6 weeks? Screening programmes are expensive but it is important to calculate both costs and benefits appropriately. In the case of EHBA, the potential savings reflect not only the costs of liver transplantation, but also the prevention of brain damage due to intracranial bleeding associated with other forms of liver disease and, most importantly, a great deal of parental stress and grief and children's suffering. There is a recent tendency to assume that a screening programme must be cheaper than the health care costs of the condition it aims to discover. Prevention is better than cure – so it does not have to be cheaper.

Criterion 10 – case finding may need to be a continuous process

Continued vigilance and repeated screening may be necessary because new cases appear continuously in the population. In this situation, however, each successive screening procedure might have a decreasing chance of detecting new cases and an increasing probability that screen failures will be false positives. Suspicion that the screening test itself is inadequate or that the standard of testing is poor is not a valid reason for repeated screening.

Would screening at more than one point in time be needed for EHBA? The age of presentation varies and some cases may not be recognisable in the first two weeks of life.[16] A case could therefore be made for any screening to be deferred until 4 weeks of age, thus reducing the number of false positives yet still meeting the deadline at 6 weeks beyond which treatment is less effective.

Conclusion

In the case of EHBA and other liver diseases of infancy, we need to determine the sensitivity and specificity of the candidate screening procedures. The direct measurement of these, in a condition that occurs in each district only once every few years, would need a nationwide study and would be more expensive than can currently be justified. Less ambitious studies may help. The sensitivity could be estimated from analysis of early symptoms and signs, and their evolution, in an unselected series of cases of EHBA and other liver disorders. The specificity could be assessed by introducing the candidate screening procedures in one or two districts.

Developing a good screening test is only a small part of the challenge. Anxiety must be minimised by the provision of efficient diagnostic services, adequate information, and continuing support. In addition, a screening programme will heighten public awareness about breast milk jaundice and efforts will be needed to avoid further falls in the rate of breast feeding.

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