Title
Management of Febrile Infants Less than 60 Days Old: A Decision Analysis

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Publication Date
1991-04-01

Management of Febrile Infants Less than 60 Days Old:
A Decision Analysis

By

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B.S. (Stanford University) 1988

THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

HEALTH AND MEDICAL SCIENCES

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA at BERKELEY

Approved:

Chair: ..... MAY 14, 1991
Date

..... 5-13-91

..... 5-14-91

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I would like to dedicate this thesis to my parents, Julie, and my classmates, without whom this could not have been written.

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ACKNOWLEDGEMENTS

I would like to thank Robert Pantell and Neil Halfon. They dedicated much time, effort, and good advice. I would also like to thank the other members of my thesis committee, Jeffrey Gould (Public Health, UC Berkeley) and Richard Scheffler (Health Economics, UC Berkeley), for providing their different perspectives during the development of my thesis.

A Brief Review of Decision Analysis

Historical perspective

Decision analysis emerged from operations research in the 1950s and spread rapidly when other disciplines began to recognize its power for structuring complicated decision problems and performing meaningful analyses. The medical community began to recognize its potential as an aid to decision-making more than thirty years ago, its origins sometimes being traced to a 1959 Science article [Ledley]. The number of publications employing decision analysis increased gradually until 1975, when the New England Journal of Medicine published a special issue featuring clinical decision analysis. Since then, several hundred studies employing decision-analytic theory have appeared in the medical literature, often as feature articles in important medical journals.

As the field of medical decision making matures, the proportion of papers describing method and theory decreases, while the proportion involving clinical application increases. Although the earliest and the most common applications addressed clinical problems in cardiology and surgery, current publications include clinical pathology, endocrinology, gastroenterology, genetics, infectious disease, nephrology, neurology, nuclear medicine, obstetrics-gynecology, oncology, ophthalmology, pediatrics, psychiatry, pulmonary medicine, radiology, rheumatology, and public health vaccinations [Kassirer]. Several major textbooks of internal medicine have included chapters on decision analysis, and several years ago the Association of American Medical Colleges recommended adding this material to the medical school curriculum. As a result, policy researchers, clinicians, and educators are beginning to use the approach for decision support.

Uses

Decision analysis has been applied to a broad spectrum of clinical problems concerning individual patients, general classes of patients, and health policy recommendations. This is possible because decision models can be tailored to optimize different outcome measures from the perspective of different individuals or organizations. Analyses of individual patients incorporate their individual characteristics, risk factors, and preferences for quality of life. Analyses of general classes of patients identify important patient characteristics, classify patients according to these characteristics, and attempt to recommend optimal strategies for these classes of patients. Health policy analyses usually address the broader use of resources relative to the prevention of well-defined outcomes (such as cases of disease). All types of analyses consider the selection of tests, treatments, screening procedures, and preventive measures.

Decision analysis is particularly useful in situations in which: (1) conclusive clinical trials have not been completed or are unlikely to occur in the near future, and (2) some information is available for estimating important branching points in the decision model. Ideally, the selection of an optimal strategy would always be determined by a large-scale, randomized and double-blinded clinical trial. Unfortunately, cost, size, and ethical limitations often make such studies impossible. Conversely, if absolutely no information is available for important probabilities, and the problem is a complex application with a large number of branching points, then the decision analysis will most likely result in a large, inconclusive set of sensitivity analyses.

The decision analysis employed in this paper attempts to address a common, primary health care problem: the management of young febrile infants (age < 60 days). Primary care problems tend to involve signs and symptoms that are less quantifiable, and often involve broader categories of

diagnoses. Although they are often more difficult to model, these types of analyses are becoming increasingly common as information collection and dispersal improves, and better data becomes available. Pediatrics, for unknown reasons, has been a particularly underrepresented field in decision analysis. Several recent articles in major pediatric journals, however, may serve to break ground for future applications [Kramer, Lieu, Downs].

Recent advances

Several important methodological advances have enhanced the power and potential applications of decision analysis. These include improved techniques for designing decision models, performing sensitivity analysis, and creating utility measures. A brief description of these advances follows (references with a more in depth discussion are provided).

The basic decision tree has been the most popular method of evaluating a decision problem. One of the classic problems with decision trees has been the continual struggle to maintain trees of manageable size. The increasing use of decision analysis in more complex domains, however, has resulted in the development of methods which may overcome these limitations. One simple solution has been the use of subtrees [Lau, Pauker], which are units that may appear repeatedly within a given tree.

This, however, did not overcome a major limitation of trees in general--the fact that the branches of trees may not be directed back to a previous node. For example, if one wishes to model the lifetime of a patient with a disease in which many cyclical transitions in health status could occur, this would create a tree of unmanageable proportions. The solution has been to use models (Markov chain models) which allow patients to cycle between various health states [Beck]. The cycling is governed by fixed probabilities attached to each possible transition. To illustrate (drawing from a published cost-effectiveness study [Sonnenberg]), consider the problem of attempting to determine relevant outcomes for patients with duodenal ulcer. Throughout their lifetimes, patients may cycle through states of ulcer relapse and healing. Modelling these types of cyclic transitions is much more efficient and realistic with Markov models than with decision trees.

Another recently employed technique is modelling by network (Monte Carlo) simulation [Roberts]. In this type of simulation, hypothetical patients are created, which then enter a network of interconnected states. As the patient moves through the various states, information is collected about which states the patient enters, what tests and treatments are done, etc. Many patients are simulated in this fashion until statistically reliable conclusions can be drawn about the process.

The increasing complexity of medical decision problems has also necessitated the improvement of techniques for performing sensitivity analysis. As wider domains are addressed by decision analysts, increasing reliance has been placed on expert estimates. Because they may be unreliable, many researchers feel that one or two-way sensitivity analysis are inappropriate for models that include a large number of expert estimates (in a one or two-way sensitivity analysis, only one or two variables, respectively, can be varied simultaneously). For example, one recent study of nursing decisions attempted a decision analysis in which all parameters of the model were derived from subjective estimates. They felt that a one or two-way sensitivity analysis would be inadequate, and subsequently developed a method for N-way sensitivity analysis [Hughes].

Although not used widely at the present time, one type of multiple-variable sensitivity analysis simultaneously varies all estimates according to probability distributions [Critchfield, Doubilet]. Randomly determined sets of estimates are created based on the distributions, and repeated evaluations of the model are then performed. From these simulations, the mean and standard deviation of the outcome measure for each strategy can be determined, as well as the frequency with which each strategy is optimal.

Finally, important methodological advances have addressed the determination of meaningful outcome measures. One of the classic problems with the selection of outcome measures is the difficulty with quantifying all outcomes on a single scale. For example, how does one compare ten years of life with a particular disability to five years without the disability? A mathematical foundation has been developed for life expectancy, and quality-adjusted life years [Pliskin]. In addition, several methods have been developed to incorporate patient preferences into the determination of utilities [Sackett, McNeil].

Criticisms

Criticisms of decision analysis come from two different perspectives. First, there are the problems recognized by those who are knowledgeable about decision analysis. These include concerns about the theoretical validity of decision analysis, the methodology of decision trees and sensitivity analysis, and the formal methods used to produce utility measures. Although these are valid problems, these are not the concerns that have impeded the acceptance of decision analysis by the general medical community. Thus, the development of increasingly complex methodologies to address these criticisms is unlikely to ease the concerns of most physicians who have little knowledge of decision analytic theory.

Published concerns of the general medical community involve more basic issues surrounding the use of decision analysis [Schwartz, Politzer]. These include: (1) the use of incomplete or subjective data, (2) the use of outcome measures which may not be meaningful, and (3) the impracticality of applying decision analysis.

To illustrate the first concern, consider a decision model for the management of early acute myocardial infarction. The management alternatives are medical therapy, streptokinase, tissue plasminogen activator, angioplasty, or coronary artery bypass surgery. An analysis which attempts to model this decision requires the probabilities of death, congestive heart failure, and lethal arrhythmias with each intervention and without intervention, the probabilities of successful reperfusion, the probabilities of significant myocardial salvage, the probabilities of complications, the probabilities of death from complications, and the probabilities of reocclusion [Knoebel]. For complicated problems such as this, all of the necessary data is usually not available, and many expert estimates must be incorporated into the model.

Physicians, however, who contest the use of these estimates, must ask themselves what probabilities they apply in making the same decisions. A decision analysis of this problem reviews all possible sources of data, including published and possibly unpublished data, assesses the validity of such data, and makes an appropriate estimate. When studies are unavailable, specialists with long experience in the field may be consulted for estimates. Finally, when all necessary estimates are collected, they must be integrated in a proper manner. The estimates of these probabilities and their integration is a difficult task for any physician.

The second criticism concerns the use of outcome measures that may not be meaningful to the physician or patient. For example, a recent article published in Pediatrics attempted to determine the appropriateness of drawing blood cultures in older infants with fever. The outcome measure was a utility scale from 0 to 1. In this type of outcome determination, the best possible outcome (in this case, the infant is well and did not undergo venipuncture for blood culture) is assigned a value of 1. The worst possible outcome (major infection plus venipuncture) is assigned a value of 0. Based on interviews of mothers and pediatricians, an outcome of venipuncture alone was assigned a value of 0.98 (in other words, venipuncture detracted 0.02 from the best outcome). A subsequent analysis which obtained different results criticized this analysis on the basis that 0.02 was "far too great" a value to assign to a simple venipuncture. The task of assigning relative utilities to various clinical outcomes can be difficult.

Unfortunately, these types of relative values must be assigned in everyday clinical practice. For example, how do physicians and patients decide between five years of life with chemotherapy and two years of life without it? To make this decision, certainly some judgement must be made regarding the

relative value of a year of life with chemotherapy versus a year without. Decision analysis makes this relative value judgement explicit.

Finally, physicians and policy-makers who wish to apply decision analysis in daily practice often find themselves limited by its computational demands. Fortunately, several computer programs have become available for the analysis of decision trees, along with education regarding their potential medical applications. General-purpose spreadsheet models have also been adapted for use in combination with decision analysis programs. The Smalltree decision analysis program and the Excel spreadsheet program were used in the study included in this paper.

Despite these advances, the creation and application of decision models for general use remains a costly, time-consuming, and expertise-intensive process. Hopefully, the current trend of education will reduce this obstacle to the use of decision analysis.

Brief description of methodology

The following is a brief description of an application of decision analysis which assumes no prior knowledge or uses any technical or theoretical terminology. References with a more in depth discussion are provided [Weinstein, Sox]. The reader who is familiar with decision analysis may turn directly to the principal study.

Decision analysis involves six basic steps: (1) definition of the problem, (2) modelling of the decision process, (3) estimation of probabilities, (4) determination of outcome measures, (5) determination of an optimal strategy, and (6) sensitivity analysis.

(1) Defining the problem

The example we will consider comes from a published decision analysis which examined the implications of routine screening of pregnant women for the Hepatitis B virus (see figure 1) [Arevalo]. The rationale for screening is that neonates of mothers who are infected with HBV can receive the hepatitis B vaccine and immune globulin, significantly reducing transmission rates. Strong evidence exists that implicates HBV as a contributing agent in chronic active hepatitis (CAH), cirrhosis (CIRR), and hepatocellular carcinoma (HCC). Neonatal infection thus results in substantial health costs, as well as untold human suffering. The problem is to determine if the reduction in cases of neonatal transmission outweighs the substantial costs of screening all pregnant women.

(2) The decision model

Creation of the model first involves determination of the primary strategies or choices. In this example (see figure), the choices are simple: (1)

Screen or (2) Do Not Screen. Each primary choice is then extended in a tree-like manner to include all possible outcomes. Branching points in a decision tree are of two types: (1) decision nodes, which represent future points when a decision must be made between two or more choices, and (2) chance nodes, which represent future points when probability determines which events will occur.

In this example, all branching points after the initial decision node are chance nodes. First consider the option of "Do Not Screen" (bottom branch of the decision tree). Some mothers will be infected with HBV, and some will not (node 2). For mothers without HBV, no transmission is possible, and for all infants of this branch the endpoint is "HBV Not Transmitted". For mothers with HBV, transmission may occur (node 7); some infants will have "HBV Transmitted", and some will have "HBV Not Transmitted".

Now consider the option of "Screen". Again, some mothers will be infected with HBV, and some will not. For mothers without HBV, most will test negative for HBV, but some will test falsely positive, depending on the specificity of the test for HBsAg (node 4). Infants of mothers who test false-positive will be vaccinated and given immune globulin. Whether or not vaccination occurs, however, the endpoint for all infants in this group is "HBV Not Transmitted".

For mothers with HBV, most will test positive for HBV, but some will test falsely negative, depending on the sensitivity of the test for HBsAg (node 3). Infants of mothers who test false-negative are not vaccinated. In these infants, a baseline level of HBV transmission will occur, and some infants will have "HBV Transmitted", and some will have "HBV Not Transmitted" (node 6). Infants of mothers who test true positive will be vaccinated. Again, a baseline level of transmission will will occur, and some infants will have "HBV Transmitted", and some will have "HBV Not Transmitted" (Node 5). For infants who have "HBV

Transmitted", however, some will receive "Protection" by the vaccination and some will receive "No Protection" (Node 8).

All infants with "HBV Transmitted" who are not protected by the vaccination (nodes 9, 10, and 11) enter a subtree (node **). Infected neonates may have subclinical or clinical hepatitis. In either case, chronic liver disease may result (nodes 12 and 13).

Readers of the analysis must ask themselves if the model adequately represents the decision process. Have all the major strategies been included? In this example, the reader might ask why the strategy of screening only high risk mothers was not included. This strategy would be more complicated, and would have to include a definition of high risk and low risk, allow for misclassification, and have epidemiologic data regarding HBV for high and low risk groups. Have all possible outcomes been represented? In this example, infants with chronic liver disease develop CAH, CIRR, or HCC, and all other infected infants have no sequelae.

Any model of a decision process will invariably include simplifying assumptions. Each assumption must be individually assessed. What is the effect of the assumption? Which strategy does it favor? Does it significantly change the results? In this example, the analysts made the simplifying assumption that 100% of infants whose mothers test positive for HBV will be vaccinated and given immune globulin. This assumption clearly favors the strategy of routine screening.

(3) Estimation of probabilities

Each branching point following the set of primary choices has an associated probability. For example, nodes 1 and 2 represent the prevalence of HBV in pregnant women. Nodes 3 and 4 represent the sensitivity and

specificity, respectively, of the test for HBsAg. Nodes 5, 6, and 7, represent the baseline transmission of HBV at birth, and node 8 represents the protection provided by vaccination.

Probabilities come from two primary sources: (1) studies, and (2) expert estimates. When studies are used, the analyst must first attempt to collect all or most of the relevant data. Second, the analyst must evaluate the quality of the data. How was it collected? From what population? How wide are the confidence intervals? Finally, the analyst must determine how the data from several relevant studies will be integrated. Alternatively, a single, best study will be chosen (see figure 2 for probabilities included in this example).

If no adequate studies are available, the analysis must rely on expert estimates. Although notoriously unreliable, physician estimates are often the only source for making medical decisions.

The reader of a decision analysis must closely examine the validity of the probability estimates. However, if good data is not available for estimates or the reader does not agree with the expert estimates, this does not necessarily invalidate the results. All probabilities should be subject to a sensitivity analysis, in which probability estimates are varied, and the effect of this variance on the results is determined (described later in more detail). If the results are not sensitive to a particular probability estimate, then that estimate does not affect the choice of an optimal strategy.

(4) Outcomes

In order to compare strategies, all outcomes must be expressed in terms of a single outcome measure. The outcome measure that is used depends on which parameters the decision-maker is attempting to maximize or minimize. Examples include dollars, hospitalization days, cases of disease, and life

expectancy. In this example, the outcome measure is dollars. The necessary costs include the screening test, the vaccination and related hospital costs, and the costs associated with the care of an infant with neonatal hepatitis (see figure 2).

(5) Optimal strategy determination

Stated simply, the value of a strategy is determined by summing the value of its outcomes, each multiplied by its probability of occurrence. In the example, the cost of routine screening of 100,000 pregnant women was $2.5 million, versus $5.5 million for not screening. At an annual national birth rate of 3.5 million, routine screening would result in a potential net savings of more than $105 million.

(6) Sensitivity analysis

In sensitivity analysis, the analyst varies all probability estimates and outcome values, and determines the effect of this variance on the results. In the example, we can test the effects of varying the prevalence of Hepatitis B in pregnant women. The estimated prevalence in the United States is 0.2%. Clearly, as the prevalence decreases, the cost of routine screening will increase relative to the cost of not screening. The cost of routine screening only exceeded the cost of no screening when the prevalence was reduced to 0.06% (this is called the threshold probability). Because the threshold probability is well below the observed probability in the United States, we can safely conclude that the choice of optimal strategy is not affected by varying the prevalence.

The purpose of sensitivity analysis is two-fold. First, it determines if the selection of an optimal strategy is changed by varying an estimate over a

reasonable range. If this is the case, then the decision as to which strategy is optimal may not be well-defined. Secondly, the analysis determines which estimates have the greatest effect on results. This information is important in directing further research. Future studies, if necessary, should be directed at collecting better data for variables which have the greatest effect on the selection of an optimal strategy.

Management of febrile infants: A decision analysis

Abstract

Decision analysis was used to compare the clinical and cost-effectiveness of two strategies in the management of young febrile infants (age < 60 days) without an identifiable source of infection. The strategies were: (1) Hospitalize and give intravenous antibiotics to all infants (**Hosp/Rx**), and (2) Perform a screening evaluation (clinical appearance, CBC, and urinalysis), hospitalize and give intravenous antibiotics to high risk infants, and send home low risk infants with follow-up (**Screen**). Strategy (1) is the official policy of many pediatric centers, and strategy (2) has been suggested as an alternative in recent literature.

Disease prevalence, test sensitivity and specificity, and other probabilities were estimated from published epidemiologic studies. Physician estimates were used when studies were not available. Hospital costs were based on hospital charges at Children's Hospital in Oakland, California. All probabilities and costs were subject to sensitivity analysis.

The principal outcomes of concern were major bacterial infection (meningitis or sepsis), and the resulting permanent complications (neurologic sequelae or death). Given 100,000 febrile infants without an identifiable focus of infection, **Hosp/Rx** resulted in 1200 cases of major bacterial infection, of which 600 resulted in permanent complications, and cost $518.8 million. **Screen** resulted in 1288 cases of major bacterial infection, of which 691 resulted in permanent complications, and cost $280.3 million. **Hosp/Rx** thus prevented 88 cases of major bacterial infection at a cost of $2.71 million/case, or 91 permanent complications at a cost of of $2.61 million/case.

According to our estimates, a previously healthy febrile infant (age < 60 days) presenting without a focus of infection has a 1.2% chance of having or developing a major bacterial infection if hospitalized and treated with IV antibiotics. Using a strategy employing a simple screening evaluation combined with good follow-up only increases that chance to 1.288%, an increase of less than 0.1%. The cost of this small increase in risk is extremely high.

Background

Fever in young infants (age < 60 days) is a common primary care problem. It can be indicative of a serious underlying infection such as meningitis or septicemia, and is of great concern for parents and physicians. Although no prospective study of the incidence of febrile illness in the first few months of life has been done, several studies have documented that between 10 and 15% of young infants seen by physicians have temperatures over 37.8C (100.0F) [Pantell, Klein].

Despite the significance of the problem, no universally accepted management policy exists. The official policy of many pediatric centers includes a complete septic workup (complete blood count, blood culture, urinalysis, urine culture, chest x-ray, and lumbar puncture with cerebrospinal fluid analysis and culture), hospitalization, and intravenous antibiotics begun presumptively until culture results are negative for 48-72 hours. This approach has also been advocated in the literature as a universal policy [Long].

Considerable variability, however, exists in the actual practice at pediatric centers and among private physicians. Although reports vary widely, among private practitioners, 10-50% report routine hospitalization and IV treatment, 50-90% report using CBC and urinalysis, 25-40% chest x-ray, and 15-50% lumbar puncture [Pantell, Greene]. Even at pediatric centers, a third or more young, febrile infants may not be hospitalized [DeAngelis].

The conservative management policy of hospitalizing and treating all infants has been favored for several reasons. First, it has long been accepted that young infants do not manifest the typical signs and symptoms of serious illness, and that discerning clinical evaluation cannot be performed. The evidence for this belief, however, has been inconsistent. One early study [Roberts], reported that one of nine bacteremic infants was judged to be

clinically well, and concluded that a conservative policy was justified. A more recent study [Baker] found that the Yale Observation Scale, which has a high sensitivity in older infants (age > 60 days) [McCarthy], misclassified 10 of 22 younger infants (age < 60 days) with serious illness as low risk. Other studies, however, have reported more reliable clinical evaluation. A meta-analysis of ten studies in the past fifteen years [Gehlbach] found that clinical appearance was 92% sensitive in detecting bacteremia in young infants.

Secondly, it is widely believed that younger infants are at greater risk for serious bacterial illness. This belief was supported by two earlier studies [Jonston, Hanninen], which reported higher rates of bacteremia for infants less than 60 days old. These studies, however, dealt exclusively with hospitalized patients, and lower rates would most certainly have been reported if infants that were sent home had been included. Two other early studies [Roberts, O'Shea] reported bacteremia rates of 9.1% (3 of 33) and 14.8% (9 of 61), but both had relatively small sample sizes. Among eight other more recent studies [Gehlbach], all with larger samples sizes, none reported a rate of bacteremia over 4%.

Finally, physicians have a strong sense that younger infants, whose immune system is not as fully developed, are less able to mount an adequate defense against bacterial infection. Most physicians would agree that younger infants are at greater risk for negative outcomes of bacterial infection.

The conflicting information that has emerged from these studies has highlighted the problems with a universal hospitalization policy. First, the high incidence of fever in young infants and the high cost of hospitalization and testing create a tremendous financial burden on both the health care system and parents. In 1982, the average cost of a hospital stay for a young febrile infant was greater than $2000 [DeAngelis].

Secondly, hospitalization and intravenous antibiotic treatment of young infants can result in unnecessary iatrogenic complications, including nosocomial infections and antibiotic allergic reactions. The only study on complications in this population reported that 19.5% of young infants admitted for fever had iatrogenic complications that resulted in additional hospital stay, diagnostic tests, or therapy [DeAngelis].

Finally, hospitalization of young infants clearly has the potential for negative psychological consequences for both the infant and parents.

For these reasons, clinicians have been attempting to define a select population of young infants which may not need to be hospitalized and given intravenous antibiotic treatment. For infants with a history of birth complications, chronic illness, or an obvious source of infection, a conservative policy is not controversial. Unfortunately, the most common diagnosis in febrile infants is fever without a focus of infection or with mild upper respiratory signs only (49.3%), followed by aseptic meningitis (12.2%), otitis media (9.0%), gastroenteritis (6.8%), pneumonia (5.4%), urinary tract infection (3.0%), and bacterial meningitis (1.3%) [Gehlbach].

For previously healthy infants without an identifiable source of infection, several studies have indicated that it may be possible to perform a screening evaluation consisting of clinical and laboratory predictors of bacteremia, and to hospitalize and treat only those infants identified as high risk. In one study which used clinical appearance, white blood cell count (high risk > 15,000 or < 5,000), band count (high risk > 500), and urinalysis (high risk > 10 WBC/hpf), 22 of 23 infants with serious bacterial infection were classified as high risk, a sensitivity of 99.3%. In a subsequent study which used similar criteria, however, only 9 of 12 infants with serious bacterial infection were classified as high risk, a sensitivity of 75% [Anbar]. Subsequently, the preceding researcher [Dagan]

conducted another study in which 22 of 22 infants with serious bacterial infection were classified as high risk (100% sensitivity).

Other laboratory criteria have also been included. One study determined that clinical appearance, WBC count (high risk > 15,000), and erythrocyte sedimentation rate (high risk > 30) would have identified all bacteremic infants included in the study (100% sensitivity) [Crain].

The common goal has been to determine the combination of tests and threshhold values that would have identified 100% of all infants with bacteremia. However, the results of these studies can be misleading for two reasons. First, although a combination of screening tests has correctly identified 100% of infants with bacteremia in several studies, the sample sizes of these studies are small, and thus the 95% confidence intervals are wide enough to include much lower sensitivities. Secondly, it is almost always possible to identify a combination of variables, given enough to select from, that in retrospect would have identified cases with very high sensitivity. Thus, studies that determine combinations of variables that would have identified all infants with serious bacterial illness must have those variables tested prospectively.

Prospective studies which mandate the collection of all necessary clinical and laboratory information from young infants and are of adequate sample size are not forthcoming in the near future. Thus, we are left with the knowledge that a screening evaluation consisting of clinical appearance and a few laboratory tests has a fairly high sensitivity, and may be an alternative to hospitalization and treatment.

The objective of this study is to compare the overall clinical and cost implications of a strategy that employs a screening evaluation and follow-up (Screen) with the currently recommended conservative policy (Hosp/Rx). The

population under consideration includes infants (age < 60 days) with fever (greater than 38.0C), who have no localizing signs, birth complications, or significant disease history. We are chiefly concerned with infants who have left the hospital/nursery in a healthy state, and return with a fever of unknown cause. The screening evaluation will include those most commonly used by physicians and suggested in the literature: clinical appearance, CBC, and urinalysis.

Structuring the Decision Model

In order for the model to be effective, it must represent the critical differences between the two strategies. Obviously, the principal problem with Screen is that infants with a potentially serious bacterial infection might be sent home. Although the physician may follow-up the infant in 24-48 hours, the delay in treatment may have irreversible consequences. The model, therefore, must adequately represent the consequences of this delay in treatment.

The principal concerns of the physician who sends home a young febrile infant include bacteremia and meningitis. Bacteremia may progress to sepsis, which can have a rapid, fatal course. Meningitis may lead to permanent neurologic consequences such as deafness or mental retardation. A short delay in the treatment of urinary tract infections, gastroenteritis, or other infections in infants who appear clinically well upon examination is less likely to have irreversible consequences.

The model will focus on the negative sequelae of a delay in treatment of infants with bacteremia and meningitis. This will be modelled as follows: (1) Infants with bacteremia who receive delayed treatment may develop a major bacterial infection such as meningitis or sepsis during the delay. (2) Infants with meningitis who receive delayed treatment will be much more likely to develop permanent complications (neurologic or death). Thus, critical outcome measures of our model will include cases of major bacterial infection (MBI), and the resulting permanent complications (PC).

Assumptions

The following assumptions were made to clarify the model. Whenever an assumption could favor either Hosp/Rx or Screen, the assumption was made in the direction that favored Hosp/Rx.

(1) Infants without an identifiable source of infection have either a viral illness, bacteremia without a major focus, or bacteremia with a major focus. Our model for bacteremia with a major focus is meningitis. Although other infections may present without an identifiable source, we are chiefly concerned with those infants that have bacteremia with or without meningitis.

(2) Because infants with meningitis presumably have bacteremia, the screening evaluation should be at least as sensitive and specific for meningitis as for bacteremia. In fact, because the infant with meningitis may appear more ill, the screening evaluation probably has a greater sensitivity and specificity for meningitis than for bacteremia. We assume conservatively that the screening evaluation has the same sensitivity and specificity for meningitis.

(3) According to the model, infants who are sent home and are persistently febrile after 24-48 hours receive a follow-up evaluation. After a 24-48 hour delay, it is more likely that physicians will be able to distinguish infants who have a viral illness, bacteremia, or a major foci of infection, either through physical appearance or lab results. We assume conservatively that the screening evaluation will have the same sensitivity and specificity after 24-48 hours.

Description of the Decision Model (see figure 2)3

In (1) Hosp/Rx, all infants are hospitalized and started on IV antibiotics. The following outcomes occur: (a) Some are bacteremic with a major focus of infection (meningitis). Their outcome is **MBI with Rx**. (b) Some are bacteremic without a major focus. Depending on the efficacy of treatment, some infants have resolving illness, and some develop a major bacterial infection (meningitis or sepsis). Their outcomes are either **Resolved** or **MBI with Rx**. (c) The remaining infants have a viral illness, and their outcome is **Resolved**.

In (2) Screen, infants are given a screening evaluation. High risk infants are hospitalized and have outcomes as in (1) Hosp/Rx. Low risk infants are sent home with instructions for close follow-up. Because of misclassification by the screening evaluation, some infants who are sent home are bacteremic with a major focus, some are bacteremic without a major focus, and the remainder have a viral illness.

At 24-48 hours, bacteremic infants with a major focus who were sent home are hospitalized and started on IV antibiotics. The outcome for all infants who are sent home with a major focus is **MBI with Late Rx**.

At 24-48 hours, bacteremic infants without a major focus are in three possible states: (a) MBI has developed. These infants are reevaluated according to the same screening procedure. Those classified as high risk are hospitalized and started on IV antibiotics, and their outcome is **MBI with Rx**. Those classified as low risk are sent home, and their outcome is **MBI with late Rx**. (b) They are febrile and persistently bacteremic, but no MBI has developed. These infants are also reevaluated. Those classified as high risk are hospitalized and given IV antibiotics. Again, depending on the efficacy of treatment, their outcomes are either **Resolved** or **MBI with Rx**. Those classified as low risk are sent home. Depending on the rate of spontaneous

resolution of bacteremia, their outcome is either **Resolved** or **MBI with Late Rx**. (c) They are afebrile and their illness has spontaneously resolved. Their outcome is **Resolved**.

At 24-48 hours, infants with viral illness are in two possible states: (a) They are febrile, and are reevaluated according to the same screening procedure. Those classified as high risk are hospitalized and given IV antibiotic treatment, and the remainder are sent home. (b) They are afebrile. The outcome for all infants with viral illness, (a) or (b), is **Resolved**.

Each outcome is extended as follows. (a) **MBI with Rx**: a fixed percentage of these infants develop permanent complications (death or neurologic). (b) **MBI with late Rx**: a greater percentage develop permanent complications. (c) **Resolved**: none of these infants have lasting effects from their illness.

All hospitalizations for MBI require 10 days, and all other hospitalizations require 3 days. A fixed percentage of all infants who are hospitalized and receive IV antibiotics will develop complications, including rash and anaphylaxis.

Probability Estimates

Probabilities were obtained from published studies and physician estimates. All values were varied in the sensitivity analysis.

To estimate the rates of bacteremia and meningitis, we could only use studies where we could distinguish infants without an identifiable focus of infection. In some cases, individual patient data was collected from authors. Five of six studies [Greene, Crain, Caspe, DeAngelis, Avner] reported a rate less than 3%, and the single study [Roberts] reporting a 10.5% rate had the smallest sample size, 38 patients without a focus. Combining infants from all 6 studies (728 total), 2.1% were bacteremic. A similar meta-analysis combining infants from studies of infants < 90 days old [Gehlbach] also found that 2.1% were bacteremic. Approximately one-third of bacteremic infants had meningitis. We estimated the prevalence of bacteremia conservatively at 3% (varied from 1% to 5%). We estimated that one-third of these infants, or 1% of the total population, would have meningitis.

Studies were used to estimate the performance of the screening evaluation only if they included "clinical impression" (based on the appearance or behavior of the infant) in their criteria. Infants were typically classified as high risk if the clinical impression was "ill" or "moderate/ambivalent", or if the infant fulfilled any one of a numerous variety of laboratory criteria. This liberal definition of high risk results in a high sensitivity for bacteremia. The specificity, however, is sacrificed. Combining four studies [Crain, Caspe, Roberts, Avner] for a total of 716 infants without a focal source, 100% (19/19) of bacteremic infants would have been identified using clinical impression, WBC and band count, and urinalysis (specificities ranged from 47% to 82%). Although two other studies would have misclassified bacteremic infants as low risk [Anbar, Baskin], these studies did not use "clinical impression" based on appearance or

behavior as a part of the screening evaluation. Clearly, however, the sensitivity of the screening evaluation is not 100%. Recognizing the difficulties with attempting to evaluate these studies, we estimate the sensitivity at 90% (varied from 80 to 99%), and the specificity at 65% (varied from 50 to 80%).

The rate of resolution of bacteremia in young infants, spontaneously or with IV antibiotic treatment, is not available from the literature. These estimates were obtained through infectious disease consultation, and were adjusted conservatively to favor Hosp/Rx. Furthermore, all estimates obtained through expert opinion were varied over extremely wide ranges. We estimate that only 10% (varied from 0 to 50%) of bacteremia in our population will resolve spontaneously, and with the remainder progressing to major bacterial infection. At follow-up (24-48 hours), we estimate that 50% (varied from 30 to 70%) of bacteremic infants will have reached their respective endpoints (resolution or major infection). With IV antibiotic treatment, we estimate that 90% (varied from 50 to 100%) of bacteremia in our population will resolve.

To estimate the rate of permanent complications from meningitis and sepsis, we used estimates from published studies of Group B Streptococcal infection. Group B Streptococcus is a predominant pathogen in the first two months of life in several geographic regions, including the United States [Hwang]. A meta-analysis of bacteremia in infants < 90 days old found that more than half of all cases were caused by Group B Streptococcus [Gehlbach]. Because our population consists of infants who have left the hospital/nursery, we are chiefly concerned with the late-onset presentation of Group B Streptococcus. Studies of the mortality rate range from 9-20% [Vesikari, Haslam, Hwang], with one expert estimating 14-18% [Ferrieri]. In the same population, estimates of neurologic sequelae from meningitis, even including mild hearing loss, range from 33-50% *of survivors* [Haslam, Hwang, Ferrieri].

We estimate the rate of permanent complications, including death and neurologic sequelae, at 50% (varied from 30 to 70%). For infants who receive delayed treatment, we conservatively estimate the rate of permanent complications at 90% (varied from 70 to 100%).

Very few studies have examined fever patterns in infants with viral illness. According to one study, about 70% of older infants with a respiratory virus infection would be afebrile at 24-48 hours. A study of infants < 60 days old, however, found that 42% of infants classified as low risk (physical exam, CBC, and urinalysis) were afebrile at < 48 hours [Dagan]. We used 42% as a baseline estimate (varied from 22 to 62%).

Estimates of rash and anaphylaxis were taken from a decision analysis of older infants. Reactions to IV antibiotics considered include rash, estimated at 0.06%, and anaphylaxis, estimated at 0.004%.

Costs

Hospital charges were used to estimate all direct costs. Although hospital charges typically overestimate costs, these estimates were varied over extremely wide ranges in the sensitivity analysis. Hospital charges were obtained from Children's Hospital in Oakland. These were collected for all admissions of infants less than 60 days old between 1/1/90 and 12/31/90. The average cost for an infant with a discharge diagnosis of "viral infection and no other symptoms" was $5,050 (the average length of stay was 3.2 days); the cost and length of stay for an infant with uncomplicated, resolved bacteremia was comparable. The average cost for an infant with bacterial meningitis was $16,528. A complete blood culture cost $45.50, and a urinalysis $24.00. A follow-up examination, including blood culture and urinalysis cost $199.50.

Results

Table 1 shows the outcomes for a hypothetical cohort of 100,000 infants. Hosp/Rx resulted in 1200 total cases of MBI, all of which were given early treatment. Screen resulted in 1288 total cases of MBI; the increase in the number of cases was due to the 24-48 hour delay in treatment of infants with bacteremia. 118 of these cases of MBI were given late treatment; these were infants missed by the screening evaluation initially or at follow-up.

Hosp/Rx resulted in 600 permanent complications, and Screen in 691; this increase was due to: (1) the increase in the number of cases of MBI allowed by Screen, and (2) the late treatment of MBI allowed by Screen.

Screen resulted in fewer hospitalizations, and thus also had fewer cases of rash and anaphylaxis, and a lower total cost. A substantial number of infants (49.7%), however, were hospitalized because of the poor specificity of the screening evaluation.

Table 2 shows the incremental cost-effectiveness ratios. Incremental cost-effectiveness ratios represent the additional cost/case of one strategy (Hosp/Rx) over another strategy (Screen). Ratios were calculated per case of MBI prevented, and per permanent complication prevented. For each case of MBI prevented, Hosp/Rx cost $2.71 million and resulted in 571 additional hospitalizations. For each permanent complication, Hosp/Rx cost $2.61 million and resulted in 551 additional hospitalizations.[1]

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[1] Typically, cost-effectiveness ratios are calculated by comparing each strategy (Hosp/Rx and Screen) with a strategy of "No Intervention" (send all infants home). "No Intervention", however, is not a viable strategy. The intent of using the incremental cost-effectiveness ratio was to allow a direct comparison between Screen and Hosp/Rx. These ratios are indicative of the impact of using Screen versus Hosp/Rx.

Sensitivity Analysis

We varied all probability values (Table 3) and costs (Table 4) over reasonable ranges, and evaluated their effect on the results. The values which were derived from expert estimates were varied over the widest ranges. The results of greatest concern were: (a) the number of cases of MBI prevented, (b) the number of permanent complications prevented, (c) the cost/case of MBI prevented, and (d) the cost/permanent complication prevented. When varied over their respective ranges, the variables that had the greatest effect on all four results were: (a) the prevalence of bacteremia, and (b) the sensitivity of the screening evaluation. The effects of varying these two variables is graphically represented (see figures ~~3, 4, 5 and 6~~ 4, 5, 6 & 7). Again, results are expressed for a hypothetical cohort of 100,000 febrile infants.

Although an increased prevalence results in an increase in the number of cases of MBI for both Hosp/Rx and Screen, the increase is greater for Screen. However, even at a 5% prevalence, Hosp/Rx only prevents 6.8% of the cases of MBI allowed by Screen; Hosp/Rx allows 2000 cases of MBI and Screen allows 2147 cases. The cost of preventing these cases at a prevalence of 5% is still $1,586,914/case of MBI. Furthermore, the flattening slope of the graph indicates that the additional cost/MBI of Hosp/Rx will remain high even at prevalences that are much higher than any study has demonstrated.

As expected, a decreased sensitivity results in an increase in the number of cases allowed by Screen. However, even at a low sensitivity of 80%, Hosp/Rx only prevents 13.8% of the cases of MBI allowed by Screen; Hosp/Rx allows 1200 cases of MBI and Screen allows 1392 cases. The cost of preventing these cases at a sensitivity of 80% is still $1,236,095/case of MBI. From the graph, it is clear that if the sensitivity of the screening procedure was above 95%, the additional cost of Hosp/Rx over Screen would be staggering.

This demonstrates the great importance of the sensitivity of the screening procedure.

The effect of varying prevalence and sensitivity was greater than for all other variables. The effect of varying specificity is included for comparison (see figures 7 and 8).

Discussion

According to many investigators, there exists a need for studies to determine the consequences of sending home young febrile infants who do not appear clinically ill or meet high risk screening laboratory criteria. In this analysis, we conservatively assumed that 90% of bacteremic infants would develop meningitis or sepsis if not treated, and that 90% of infants with meningitis or sepsis who received delayed treatment would either die or have permanent neurologic dysfunction. Even if future studies reveal effects of this magnitude, the combination of a screening evaluation and follow-up resulted in only a small increase in cases of MBI and permanent complications. According to our estimates, a previously healthy febrile infant (age < 60 days) presenting without a focus of infection has a 1.2% chance of having or developing a major bacterial infection if hospitalized and treated with IV antibiotics. Using a strategy employing a simple screening evaluation combined with good follow-up only increases that chance to 1.288%, an increase of less than 0.1%.

Efforts are also underway to determine the combination of clinical and laboratory predictors with the highest sensitivity for bacteremia and major bacterial infection. Past research suggests that in order to obtain adequate sensitivities, a number of clinical and laboratory predictors must be combined. Unfortunately, unless better tests become available, the use of these multiple triggers to hospitalization and treatment will result in screening evaluations with high sensitivities and low specificities. As shown in the analysis, the use of such a screening evaluation still results in many unnecessary hospitalizations.

Results of the sensitivity analysis reveal that the sensitivity of the screening evaluation is the single most important variable in determining the number of additional cases allowed by Screen and the additional cost/case of MBI. Certainly, better knowledge of the sensitivity of screening evaluations for

bacteremia and meningitis is necessary. However, even with the moderate sensitivity and specificity assumed in this analysis, the additional cost incurred by hospitalizing and treating all young febrile infants to prevent each major infection or permanent complication was extremely high.

Indirect costs not included in the analysis include: (1) The long-term costs of permanent complications. (2) The cost of complications of hospitalization and intravenous antibiotic treatment. (3) The long-term effects of hospitalization on infants/children. (4) The increased use of the medical system as a result of hospitalizing all infants. (5) The increase in microbial resistance as a result of treating all infants.

It is possible to obtain rough estimates of long-term morbidity and mortality costs based on cost-of-illness estimates which have been summarized from a number of publications [Rice]. Morbidity costs include earnings lost by people who are unable to work because of illness or disability, and costs associated with caring for people unable to perform basic housekeeping functions. The lifetime morbidity cost of a single person with a disease of the nervous system or sense organ is approximately $700,000. Even if this cost is included, the additional cost/permanent complication incurred by Hosp/IV is still almost $3,000,000.

Other indirect costs, (2) through (5), were not included in the analysis and would be difficult to calculate. However, each of these costs that were not included would increase the relative cost of Hosp/Rx versus Screen. Thus, we can assume, given our conservative probability estimates and the absence of these indirect costs, that the cost-effectiveness ratios given in this study probably underestimate the actual values.

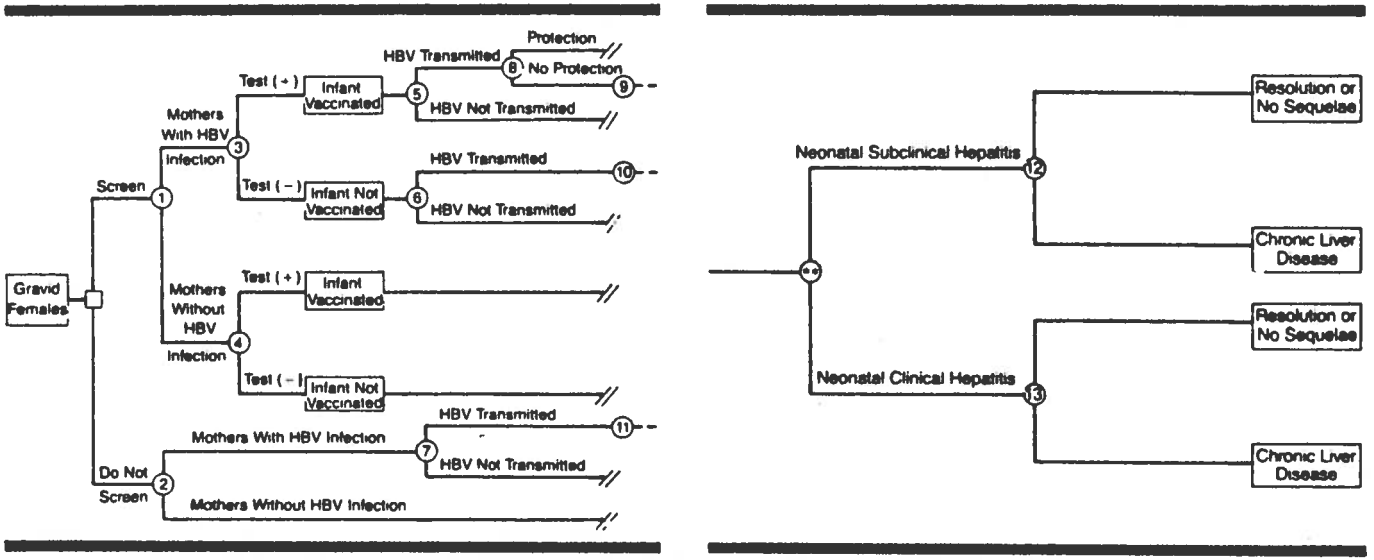


Fig 1.—Decision tree depicting outcomes for screening or not screening pregnant females for hepatitis B surface antigen. Left, Decision tree for Perinatal Hepatitis B Screening and Immunization Program. HBV indicates hepatitis B virus; circles, chance node; and square, decision node. Right, Continuation. Double asterisks indicate nodes 9 to 11.

FIGURE 1

FIGURE 2

Table 1.—Probabilities Used in Decision Analysis

Outcomes	Baseline Probability	Accepted Range of Probability	Source
Mother with +HBsAg*	.002	.001-.15	Hoofnagle and Alter,[1] Advisory Committee on Immunization Practices,[2] Maison et al,[25] Malecki et al[26]
HBsAg test			
Specificity	.980	.96-.99	Holland[27]
Sensitivity	.975	.95-.99	
Probability of perinatal transmission	.425	.125-.90	Beasley et al,[9] Wong et al[10]
Efficacy of immunization	.90	.85-.95	Beasley et al,[9] Wong et al,[10] Stevens et al[11]
Probability of acute hepatitis in neonates	.025	.02-.03	Dealplane et al,[17] Sinatra et al[18]
Probability of death from chronic liver disease	.25	.25-.30	Beasley,[3] Beasley et al[19]

*HBsAg indicates hepatitis B surface antigen.

Table 3.—Cost Assumptions* Used in Decision Analysis

Variable†	Cost, $
Screening test for HBsAg	20
Hepatitis B vaccination	
HBIG, 0.5 mL, IM	15
Hepatitis B vaccine, 3 doses at 10 μg/dose	50
Physician visit at 2 mo for second vaccination	35
Test for HBsAg at 12 to 18 mo	20
Hospitalization for neonatal hepatitis	2500
Total care per case of chronic liver disease	27 512

*Cost in 1985 dollars.
†HBsAg indicates hepatitis B surface antigen; HBIG, hepatitis B immune globulin; and IM, intramuscularly.

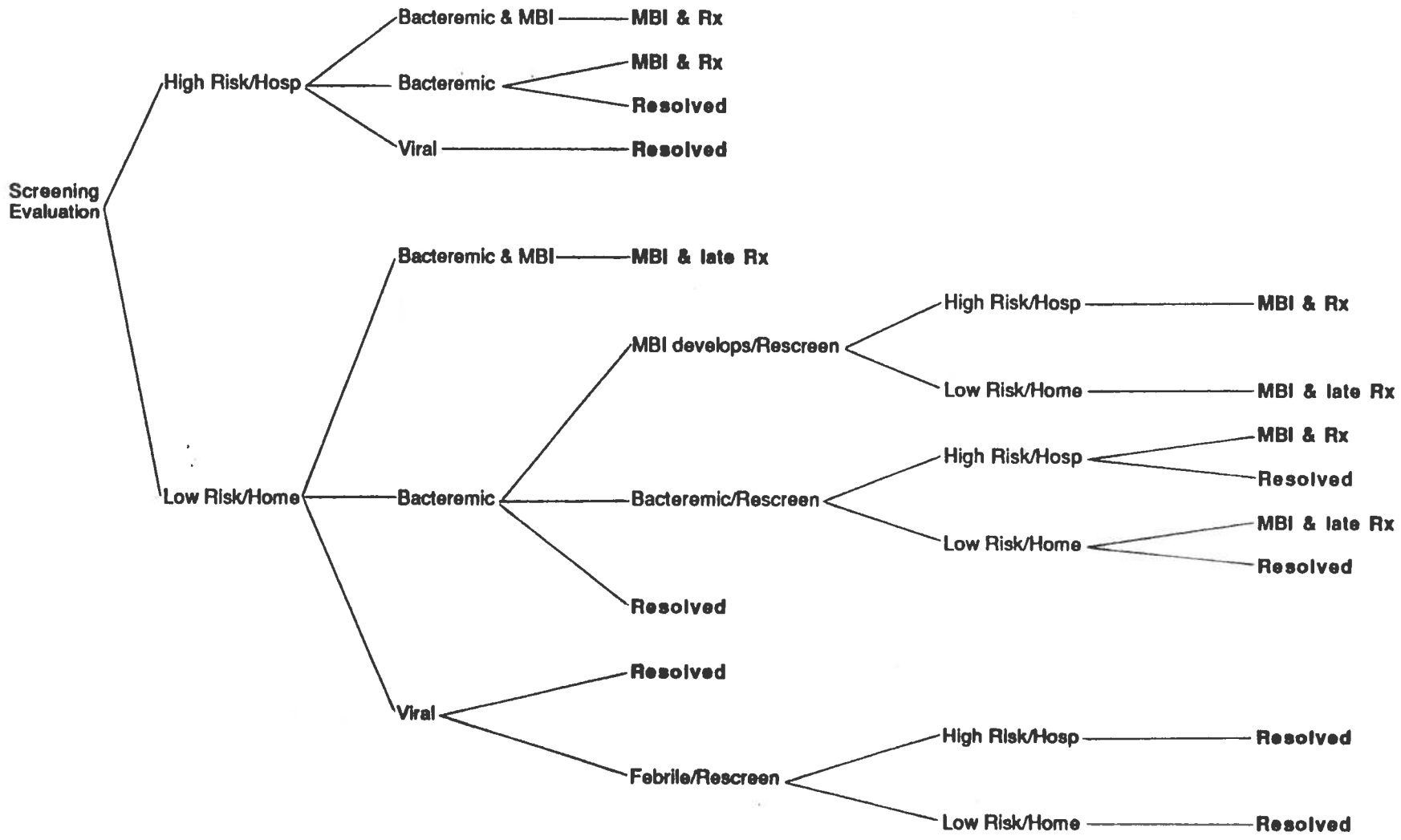


FIGURE 3: DECISION TREE FOR SCREEN

TABLE 1

Incremental cost-effectiveness ratios of Hosp/Rx over Screen under baseline assumptions

Dollars/MBI	$2,702,983
Dollars/PC	$2,614,896
Hospitalizations/MBI	571
Hospitalizations/PC	551
Hospital days/MBI	1706
Hospital days/PC	1647
Rash/MBI	34.3
Rash/PC	33.1
Anaphylaxis/MBI	0.23
Anaphylaxis/PC	0.22

TABLE 2

Clinical outcomes of a hypothetical cohort of 100,000 febrile infants without a focus of infection under baseline assumptions

	Hosp/Rx	Screen
Major Bacterial Infection		
Total Cases	1200	1288
Cases with late Rx	0	118
Permanent Complications	600	691
Hospitalized	100,000	49,738
Hospitalization days	308,400	158,230
Rashes	6000	2984
Anaphylaxis	40	20
Cost of hospitalization	209.60	109.78
Cost of screening	0	1.00
Cost of follow-up	0	3.67
Total cost (millions of $)	209.60	114.45

TABLE 3

Probability estimates and sensitivity analysis ranges

Variable	Estimate	Range
prevalence	3%	1-5%
screening evaluation:		
sensitivity	90%	80-99%
specificity	65%	50-80%
Bacteremia & Rx:		
% developing MBI	10%	0-50%
Bacteremia & no Rx:		
% developing MBI	90%	50-100%
MBI & Rx:		
% developing PC	50%	30-70%
MBI & late Rx:		
% developing PC	90%	70-100%
% reaching endpoint (resolution or MBI)		
at follow-up	50%	30-70%
resolution of viral illness		
at follow-up	42%	22-62%

TABLE 4

Costs and sensitivity analysis ranges

Variable	Estimate	Range
Hospitalization		
Bacterial meningitis	$16,528	$10-20,000
Viral/Resolved Bacteremia	$5050	$3-7000
Screening Evaluation (CBC+UA)	$70	$10-130
Follow-up Examination	$200	$50-300

FIGURE 4

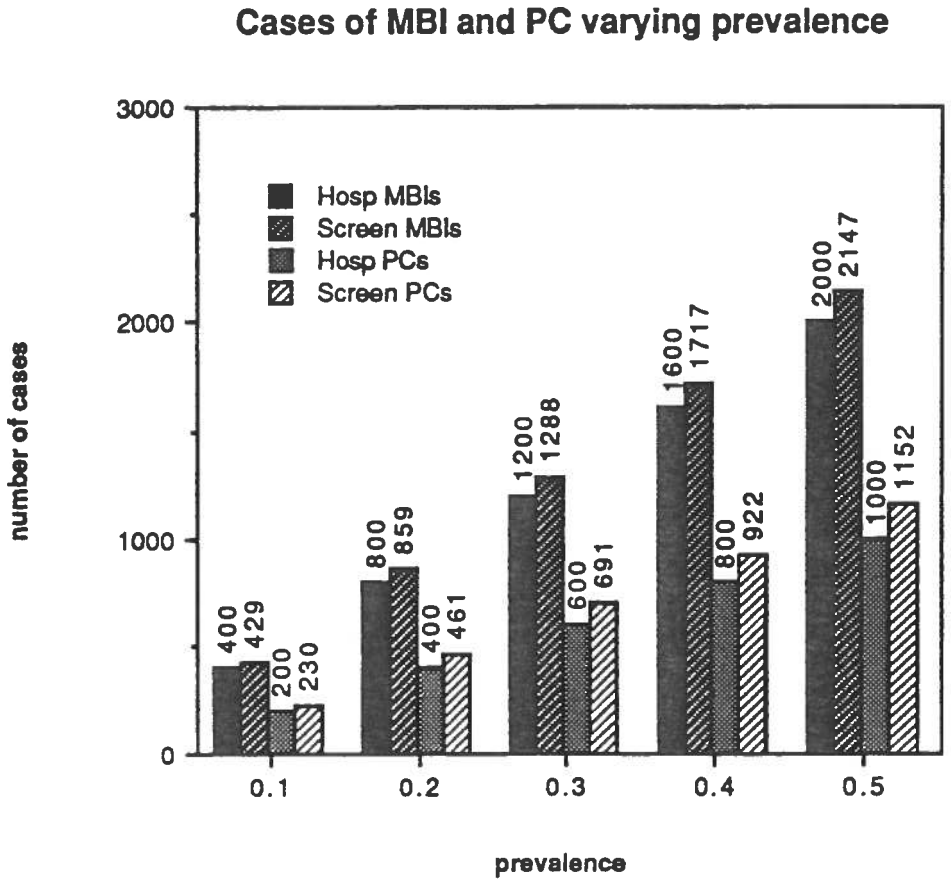

Cases of MBI and PC varying prevalence
number of cases
3000
2000
1000
0
Hosp MBIs
Screen MBIs
Hosp PCs
Screen PCs
400
429
200
230
800
859
400
461
1200
1288
600
691
1600
1717
800
922
2000
2147
1000
1152
0.1
0.2
0.3
0.4
0.5
prevalence

FIGURE 5

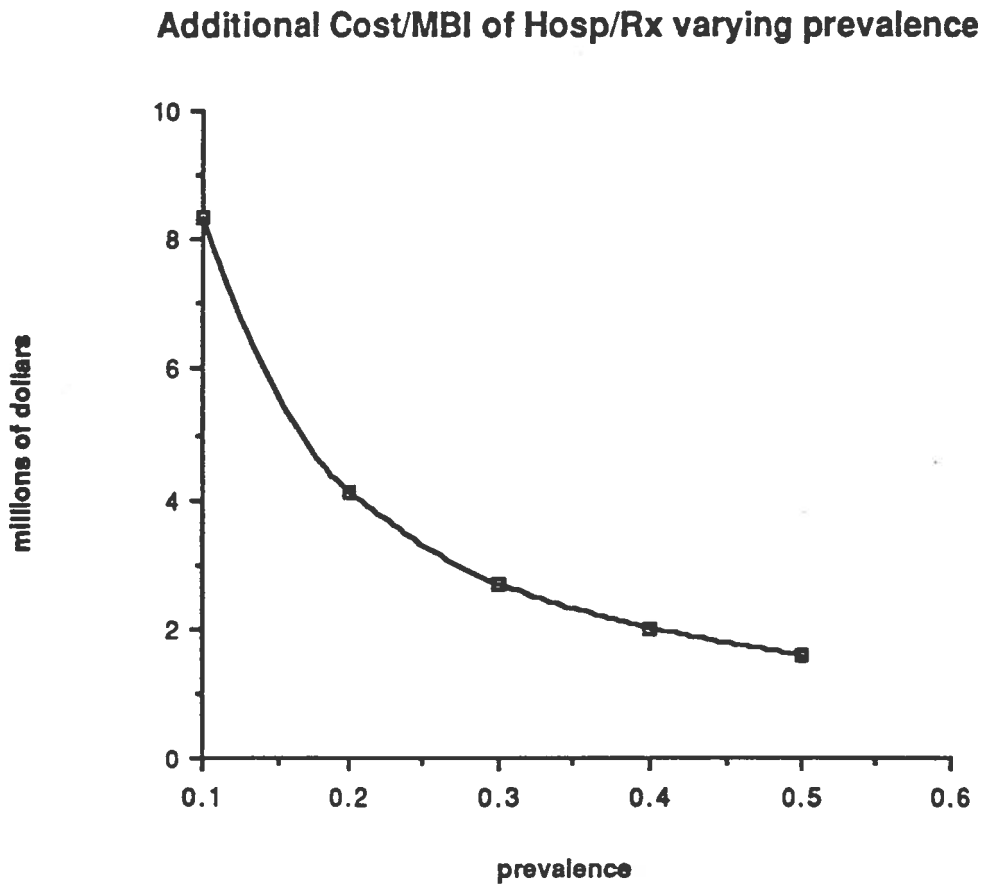

Additional Cost/MBI of Hosp/Rx varying prevalence
millions of dollars
10
8
6
4
2
0
0.1
0.2
0.3
0.4
0.5
0.6
prevalence

FIGURE 6

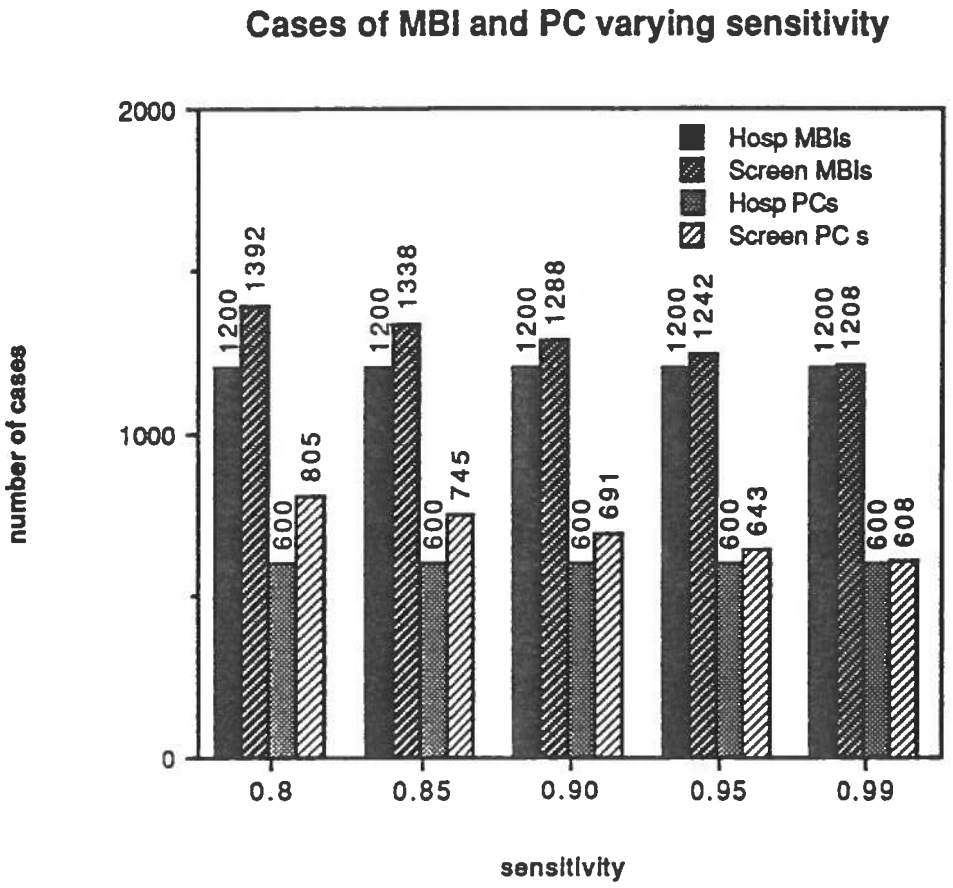

Cases of MBI and PC varying sensitivity
2000
1000
0
number of cases
Hosp MBIs
Screen MBIs
Hosp PCs
Screen PC s
1200
1392
600
805
1200
1338
600
745
1200
1288
600
691
1200
1242
600
643
1200
1208
600
608
0.8
0.85
0.90
0.95
0.99
sensitivity

FIGURE 7

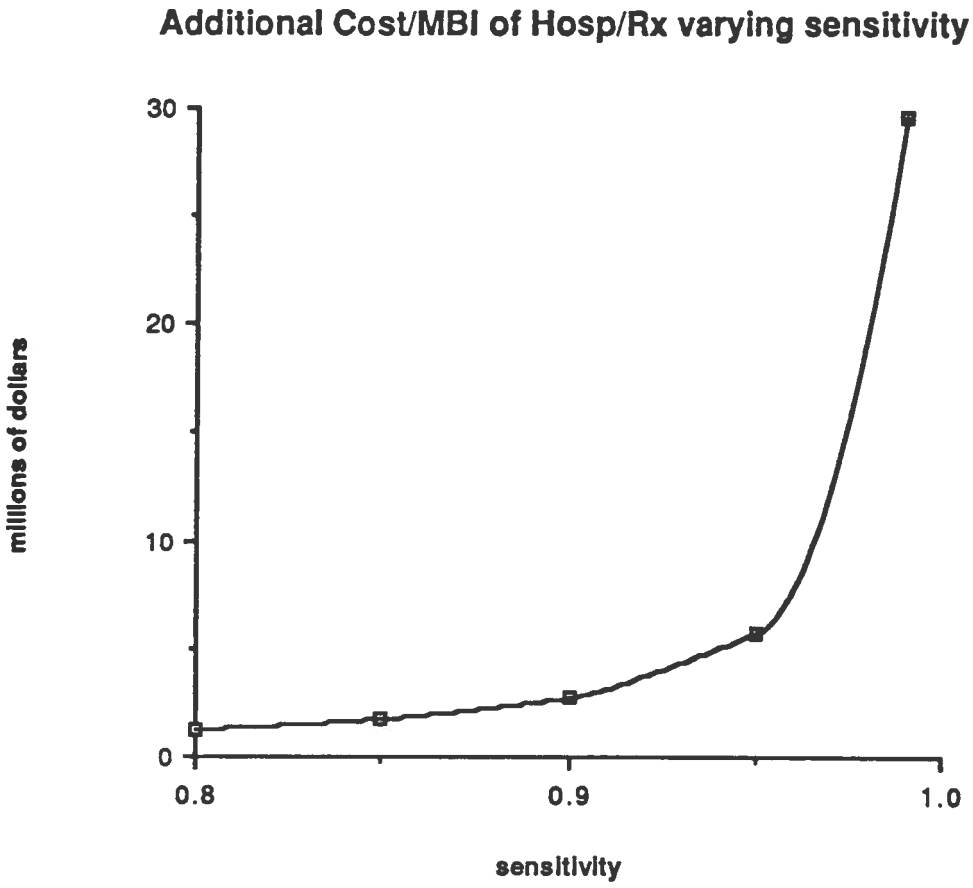
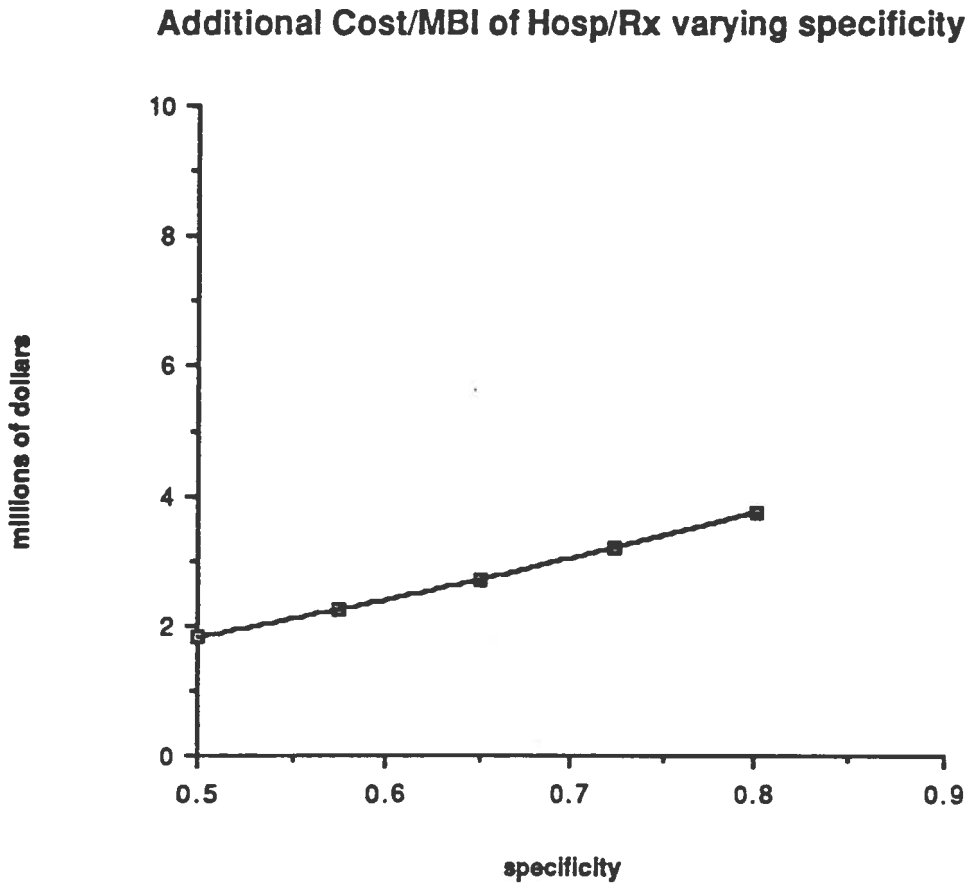

Additional Cost/MBI of Hosp/Rx varying sensitivity
millions of dollars
30
20
10
0
0.8
0.9
1.0
sensitivity

FIGURE 8


Additional Cost/MBI of Hosp/Rx varying specificity
millions of dollars
10
8
6
4
2
0
0.5
0.6
0.7
0.8
0.9
specificity

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