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Anemia Is a Poor Predictor of Iron Deficiency Among Toddlers in the United States: For Heme the Bell Tolls

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Anemia Is a Poor Predictor of Iron Deficiency Among Toddlers in the United States: For Heme the Bell Tolls

Keith C. White, MD

ABSTRACT. *Context.* **Many toddlers in the United States have their hemoglobin (Hb) measured periodically. Is this worthwhile?**

Objective. **To determine if the presence of anemia correctly diagnoses iron deficiency (ID) and if the absence of anemia correctly rules out ID in young children.**

Methodology. **An analysis of data from the US National Health and Nutrition Examination Survey III (1988–1994) was performed. Subjects were children 12 to 35 months old for whom complete blood counts and cardinal measures of iron nutrition (ferritin, transferrin saturation, and free erythrocyte protoporphyrin) were reported.**

Results. **In the US National Health and Nutrition Examination Survey III, the prevalence of ID ranged from 6% to 18% in various subpopulations of toddlers. In the general population, the positive predictive value of Hb concentration ([Hb]) <110 g/L for ID was 29% (95% confidence interval [CI]: 20–38%), and the sensitivity was 30% (95% CI: 20–40%). Changing the diagnostic cutoff point to [Hb] <107 g/L resulted in a positive predictive value of 38% (95% CI: 24–52%) but lowered the sensitivity to 15% (95% CI: 7–22%).**

Conclusions. **ID remains common in the United States. In agreement with other reports, anemia in toddlers in developed countries is more likely to be due to causes other than ID. Conversely, most children with ID are not anemic. Many false-positive and false-negative results render the measurement of Hb a screening test of relatively little value. The current detection strategy needlessly treats and retests many children without ID and leaves many iron-deficient toddlers unattended.** ***Pediatrics*** **2005;115:315–320;** ***African Americans, anemia, child, preschool, evidence-based medicine, hemoglobin, Mexican Americans, iron deficiency, iron-deficiency anemia, NHANES III, positive predictive value, poverty, sensitivity, toddlers, United States.***

ABBREVIATIONS. Hb, hemoglobin; ID, iron deficiency; WIC, Supplemental Nutrition Program for Women, Infants, and Children; NHANES, National Health and Nutrition Examination Survey; IDA iron-deficiency anemia; PPV, positive predictive value; BRR, balanced repeated replication; EPP, erythrocyte protoporphyrin; MCV, mean corpuscular volume; CI, confidence interval.

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Many of the 8 million American children between 1 and 3 years old routinely have their hemoglobin (Hb) measured. Economically disadvantaged children are more likely to be screened for iron deficiency (ID) by this method. Many Medicaid programs require universal screening, and the Supplemental Nutrition Program for Women, Infants, and Children (WIC) program requires a Hb determination for children to enroll. Although children in this age group are the most likely to be iron-deficient[1,2] and are least likely to meet their recommended intakes for iron,[3,4] there is scant evidence to support this current practice. The National Health and Nutrition Examination Survey (NHANES) II (1976–1980) showed that the likelihood of an anemic child 1 to 5 years old being iron-deficient was <50%.[5] The utility of this test has not been considered in 20 years.

The prevalence of ID and iron-deficiency anemia (IDA) in NHANES III was reported previously.[1] That study did not report the prevalence of anemia of all causes, permitting the calculation of the positive predictive value (PPV) of anemia for ID. Was the PPV different from NHANES II? The previous study did not apply demographic stratification. Is the sensitivity of screening with the Hb test higher in children living below the poverty line? How does the usefulness of the test compare in children from different ethnic groups?

This is the first consideration of the prevalence of ID, IDA, and anemia of all causes in young children living in different economic strata and different ethnic groups. The resulting statistics are intended for practitioners.

MATERIALS AND METHODS

The NHANES III (1988–1994) was 1 of a series of surveys designed to provide national estimates of the health and nutritional status of the US population ≥2 months old. The NHANESs are performed continuously across the United States in specially designed medical examination centers. They are excellent sources of data of very high quality.

A CD-ROM of public-use data files from NHANES III was obtained from the National Technical Information Service (www.ntis.gov/fcpc). The Statistical Program for the Social Sciences (SPSS) version 11.0[6] and Wesvar 4.2[7] were used to analyze the data.

The US NHANES[8] is a multistage, stratified population survey (rather than a random sample), which is a common sampling design. Populations of particular interest are oversampled to assure their representation. For example, black children comprised 29% of children tested in NHANES III, although they represented 17% of the population in this age range in 1988-1994. Children living below the poverty line comprised 40% of the children surveyed but represented 27% of the toddlers in the United States in those years. The methodology of NHANES acknowledges these biases and assigns sampling weights, numerical factors that are inversely proportional to the likelihood of a subject being selected. Other weights are assigned to correct for nonresponse and adjustments in estimates of the census.

A full sample weight and 52 partial sampling weights are calculated for each study subject. Balanced repeated replication (BRR)[9] is a statistical method recommended to calculate estimates for the NHANES.[8] The Fay method, with $K = 0.3$, was used.

Subjects were 12 to 35 months (inclusive) old at the time of examination. The poverty index ratio was used to stratify the subjects according to their families' incomes. NHANES assigned the poverty index ratio based on a family's self-reported income and size, using tables published each year by the Bureau of the Census. The race/ethnicity classification of the subjects was based on self-report.

All subjects had complete blood counts and cardinal measures of iron nutrition (ferritin, transferrin saturation, and free erythrocyte protoporphyrin [EPP]). Concentrations of lead in serum were also considered when available. According to the documentation accompanying the NHANES, blood was collected by venipuncture and samples were processed at the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention. Analyses were performed according to detailed plans.[10]

In this study, ID was diagnosed if ≥2 of the following pertained: ferritin <10 μg/L, transferrin saturation <10%, and EPP >1.42 μmol/L red blood cells. Anemia was diagnosed if Hb concentration ([Hb]) was <110 g/L. IDA was diagnosed if anemia accompanied ID. The National Center for Health Statistics of the US Centers for Disease Control and Prevention[1,2] and other authorities[11] use this criterion standard; it was developed by the Expert Scientific Working Group.[12]

RESULTS

Table 1 is a description of laboratory and demographic characteristics of children from the general population of US toddlers without ID ($n = 1149$) and with ID ($n = 140$). The estimates followed BRR. Children with ID had statistically lower concentrations of Hb (on the average lower by 5% of the mean value), were more likely to be from households with incomes below the poverty line, and were more likely to have parents who described themselves as Mexican American. Children from non-Hispanic white households had a smaller chance of being iron-deficient.

Table 2 reports the prevalence of ID, IDA PPV, and sensitivity for various strata of toddlers. The reporting guidelines for NHANES suggest that, optimally, a minimum sample size of 30 per cell be used to report estimates and that coefficients of variation should be <30%. The guidelines also recommend that no estimate should be suppressed simply because it is potentially unreliable (in a statistical sense). Estimates that do not meet the most stringent level of reliability are marked with asterisks.

Consideration was given to ID defined by a previous biochemical definition (low % transferrin saturation, low mean corpuscular volume [MCV], and high [EPP]).[12] Using the older standard, for the general population of toddlers in the United States, the PPV for [Hb] <110 g/L for ID was 0.53 (0.37–0.68) and the sensitivity was 0.23 (0.18–0.28).

Figure 1 depicts the relative distributions of the 1289 subjects from NHANES III who had complete values for [Hb], [ferritin], % transferrin saturation, and [EPP]. Of these subjects, 140 could be classified as ID (Fig 1, bottom half), 48 had IDA (Fig 1, lower-left quadrant), and 106 had anemia without ID (Fig 1, upper-left quadrant). The histogram compares the distributions before the consideration of sampling weights and qualitatively displays the overlap of iron-sufficient and iron-deficient populations.

Figures 2 and 3 depict how estimates of the PPV and sensitivity vary as the cutoff for [Hb] is changed. Estimates represent the general population. Decreasing the cutoff results in a modest increase in the PPV to 38% (95% confidence interval [CI]: 24–52%) but lowered the sensitivity to 15% (95% CI: 7–22%). Estimates of these variables below [Hb] = 107 g/L cannot be calculated reliably because the number of cases is <30.

Figure 4 is a Venn diagram depicting the intersections of the sets of the general US toddler population and children with ID, IDA, and anemia.

TABLE 1. Characteristics of Toddlers in Survey After Adjustment for Sampling Weights (NHANES III, Children 12 to 35 Months Old): Estimates for US General Population

Characteristic	ID⁻ ($n = 1149$)	ID⁺ ($n = 140$)
Mean [Hb], g/L	121.1*	115.0*
SD, g/dL	7.6	8.8
Serum [lead] > 10 mg/dL, %	9	10
Above poverty line, %	73†	65†
Below poverty line, %	27†	35†
Enrolled in WIC, %	19	15
Non-Hispanic white, %	63‡	43‡
Non-Hispanic black, %	17	18
Mexican American, %	10§	20§
Other ethnicity, %	10	18

* $P = .02$ by t test; † $P = .03$ by χ^2; ‡ $P = .0001$ by χ^2; § $P = .0001$ χ^2.

DISCUSSION

This Study

In the United States, a child 12 to 35 months old is considered anemic if his or her [Hb] is <110 g/L. This value is derived from a sample of toddlers from NHANES III[1] that excluded persons with biochemical evidence of ID. The distribution of Hb from venous blood was determined in 883 children who had normal values for [ferritin], transferrin saturation, [EPP], and MCV. The mean value of [Hb] was 122.0 g/L, with an SD of 7.34 g/L. Subtracting 1.65 SD from the mean results in the cutoff of <110 g/L that represents the lower 5% of an iron-sufficient population (cf Table 1). This is the standard used in daily practice.

This Gaussian definition of abnormality does not permit the calculation of the diagnostic probability that a patient has ID. That essential measure is the PPV, where PPV = true-positives/(true-positives + false-positives). One needs to know the prevalence of anemia of all causes (the denominator of this equation). Surprisingly, the prevalence of anemia of all causes was omitted in most previous reports about NHANES.[1,2] An exception was a report[13] of 9.6% prevalence for anemia of all causes in children 1 to 5 years old from the general population sampled in NHANES III. This finding compares closely with the 9% (7–12%) presented in the first row, third column of Table 2.

TABLE 2. Demographic, Nutritional, and Hematologic Descriptions of Toddlers (NHANES III, Children 12 to 35 Months Old With Known Values for [Hb], [Ferritin], [EPP], and % Transferrin Saturation)

Population Sampled (*n*)	Estimates Adjusted for Sampling Weights, % (95% CI)					
	Proportion of US Toddler Population	Prevalence of ID	Prevalence of IDA	Prevalence of Anemia (All types)	PPV of [Hb] < 110 g/L for ID	Sensitivity of [Hb] < 110g/L for ID
General US population (1289)	—	9 (7–11)	3 (2–4)	9 (7–11)	28 (20–38)	30 (20–40)
Above poverty line (681)	72 (68–76)	8 (5–10)	1 (1–2)	6 (4–8)	23 (10–36)	19* (7–31)
Below poverty line (517)	28 (24–32)	12 (7–16)	5* (2–7)	15 (9–20)	32* (21–43)	43* (27–56)
Enrolled in WIC (242)	18 (16–21)	7* (3–12)	3* (1–6)	10 (6–14)	33* (15–51)	48* (23–73)
Non-Hispanic white (410)	61 (57–65)	6* (4–9)	1* (0–2)	6* (4–9)	20* (6–35)	20* (6–34)
Non-Hispanic black (379)	17 (15–19)	10 (6–13)	5* (2–8)	18 (13–24)	28* (17–40)	53* (33–74)
Mexican American (429)	11 (9–12)	18 (13–23)	5* (3–8)	11 (7–13)	53* (35–72)†	29* (20–39)
Other ethnicities (71)	10 (7–15)	14* (4–25)	4* (0–9)	12 (4–20)	36* (11–60)	29* (3–56)

* Potentially unreliable estimates ($n < 30$).
† See "Discussion."

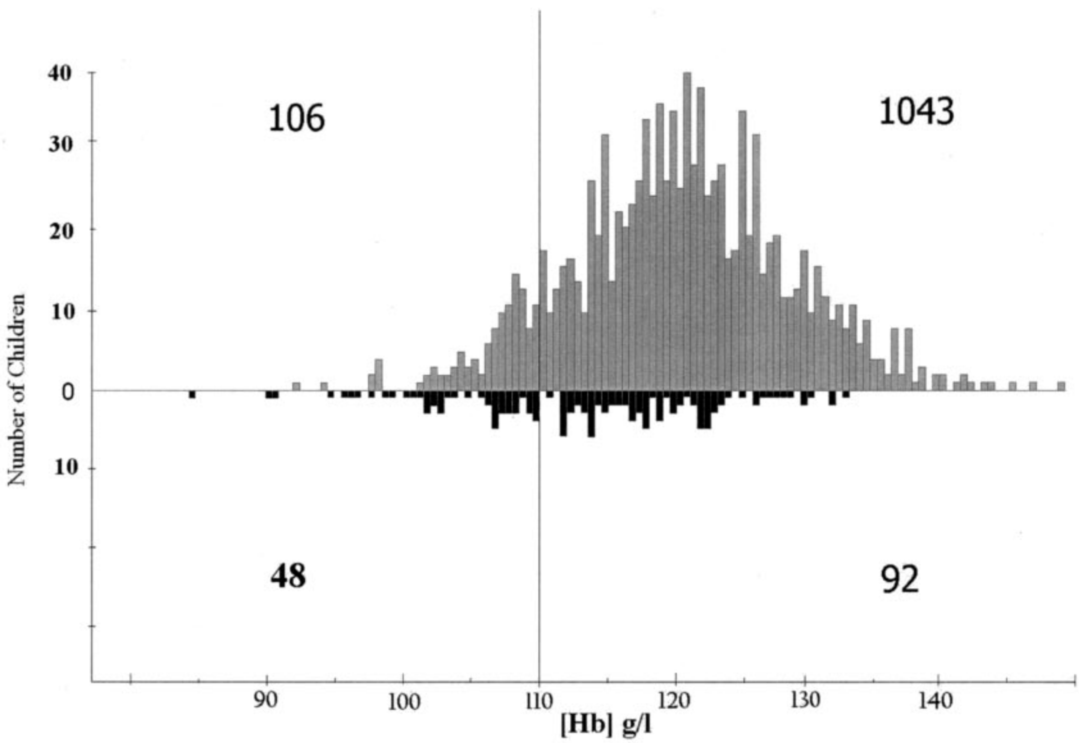

Fig 1. Comparisons of distributions of [Hb] of toddlers in US NHANES III. Grey bars indicate ID^{-}; black bars, ID^{+}. Observations are not corrected for sampling weights. The vertical line indicates the usual [Hb] defining anemia.

The results of the present study indicate that Hb is not a clinically useful test for assessment of iron adequacy among toddlers in the United States. The PPV reflects how accurately [Hb] diagnoses ID. Among the general population, an anemic toddler has 1 chance in 3 of being iron-deficient. The sensitivity of this test is of similar magnitude: a [Hb] of <110 g/L is only seen in ID one third of the time. Lowering the [Hb] used as a cutoff does increase the PPV slightly but at the cost of a lower test sensitivity. At best, the Hb test is a screening procedure of relatively little value.

Dividing the subjects into subsets does not reveal any striking difference in the utility of the test for any economic or ethnic group. The overall trend was PPV and sensitivities of ~30%. Some of the estimates are possibly unreliable, because smaller sample sizes ($n < 30$) may not allow normal approximations. For example, among Mexican American children depicted in Table 2 (indicated by †), 23 had IDA and 47 had anemia of all types. The resulting estimate of the PPV after BRR was 53% (35-72%), an estimate with a wide, unsatisfactory CI. Even large and well-conducted surveys such as NHANES III cannot provide enough statistical power to assess the utility of the Hb test with precision.

The methodology of NHANES specified collection of venous blood and analysis by carefully calibrated Coulter counters.[10] In clinical practice, capillary blood is often collected and analyzed with bench-top hemoglobinometers or by centrifuging microhematocrit tubes. Specimens obtained by these methods cannot be compared with those reported here.

The cause of the majority of anemia among the

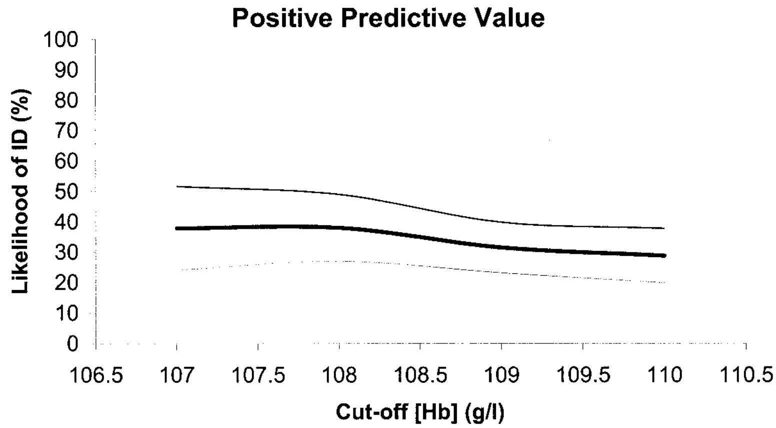

Fig 2. PPV versus [Hb] threshold: estimates and 95% CIs.

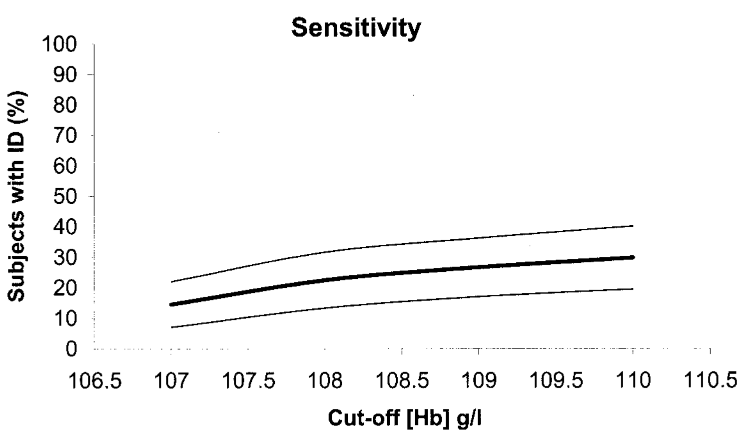

Fig 3. Sensitivity versus [Hb] threshold: estimates and 95% CIs.

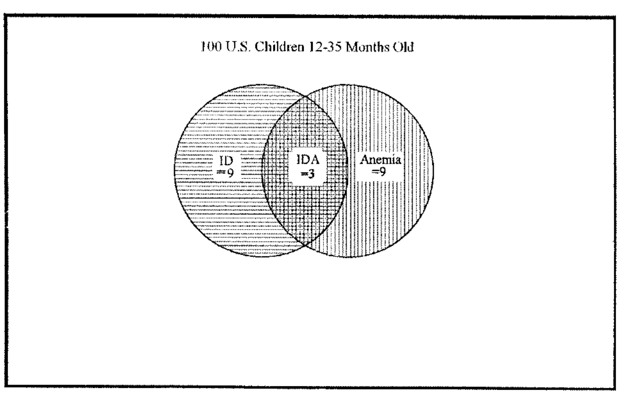

Fig 4. Venn diagram illustrating overlap of groups with ID and anemia.

children with adequate stores of iron in NHANES III cannot be explained completely from the available data. Serum folate, B_{12}, Hb electrophoresis, and reticulocyte counts were not performed in subjects in the 12- to 35-month-old age group. α and β thalassemia traits, hemoglobinopathies (such as S, C, and E traits), cytostructural abnormalities, and enzyme defects (glucose-6-phosphate dehydrogenase deficiency) are hypothetical contributors. Exact estimates of these conditions in the US population are not available. Anemia associated with acute and chronic infections[14] possibly explains many cases.

Other Populations

Limited recent data from NHANES were available at the time of writing (July 2004). The NHANES 1999–2000 data release contains complete hematologic and nutritional observations of only 319 young children, and the NHANES 2001–2002 release contains none. According to the release schedule for NHANES,[15] we will have to wait until at least 2006 to extend these studies among toddlers in the US.

Soh et al[16] performed a community-based cross-sectional survey of randomly selected, 6- to 24-month-old children in New Zealand. Their criterion for ID was the ferritin, EPP, and MCV model. Children with a C-reactive protein level of >10 mg/L (who might have suffered recent infections) were excluded from consideration. Among 169 toddlers 12 to 24 months old, 22% had [Hb] of <110 g/L, 2.5% had IDA, and 5.0% had ID without anemia. In that study, the PPV of [Hb] for ID can be calculated as 2.5%/22% = 11% (95% CI: 9–13%) and the sensitivity can be calculated as 2.5%/7.5% = 33% (95% CI: 26–40%).

A study of 488 infants from 11 European countries[17] also indicated poor utility of the Hb test. Hb, serum ferritin, MCV, transferrin saturation, and serum transferrin receptor concentrations were measured at 12 months. The prevalence of ID was 7.2%, of ID anemia 2.3%, and of anemia of all causes 9.4%. More than 40% of anemia was associated with normal iron status (all indicators of iron nutrition normal) and associated with an increased frequency of recent infections. Another 35% of anemic patients had only 1 abnormal iron indicator. Thus, at 1 year of age, the PPV of anemia for ID was 2.3%/9.4% = 24% (95% CI: 20–28%) and the sensitivity was 2.3%/7.2% = 32% (95% CI: 28–36%).

The National Diet and Nutrition Survey[18] took place in Mainland Britain in 1992–1993. It was a cross-sectional study considered to be representative of preschool children in the general population. Serum EPP was not measured in this study, so it is not possible to calculate the percentage of children who were iron-deficient by the Centers for Disease Control and Prevention definition. Blood was obtained from 1003 subjects 1.5 to 4.5 years old. Eight percent of the children had a [Hb] of <110 g/L, but only 3.4% had a low Hb with a ferritin level of <10 μg/L. Thus, the PPV of anemia for iron depletion was 3.4%/8% = 42%. Because ID is a less common condition than iron depletion (low [ferritin]), the PPV of anemia for ID in British children in that survey can be estimated at <42%.

Kazal[19] found that the hematocrit failed to detect iron depletion (low [ferritin]) in infants and toddlers in the United States. Hematocrit and ferritin concentrations were measured from capillary blood from 321 children 9 to 18 months old. All were from low-income households. Children with acute illnesses and those receiving medicinal iron were excluded from the study. Six (1.9%) of the children were anemic, but none had low [ferritin]. Fifty-one infants (15.9%) had [ferritin] <10 μg/dL, but none were anemic.

Implications

ID is as important a problem as it ever was, but 2 aspects must be recognized. First, most anemic toddlers in the United States do not have ID. Second, the majority of toddlers with ID in the United States are not anemic. Screening children in this age group for anemia misdirects our attention from these findings. Assuming that [Hb] is an accurate proxy for iron status is misleading. It gives us false assurance that children without anemia are iron-sufficient, although they may be at significant risk. No candidate test for ID (transferrin receptors,[20] reticulocyte Hb concentration,[21] or free erythrocyte protoporphyrin alone[13]) is likely to allow screening for ID in a more selective fashion than [Hb].

Iron is present in 200 to 300 enzymes and is important for health. We work to prevent ID because ID severe enough to cause IDA is associated with developmental disabilities.[22,23] It is unclear if these problems are reversible if iron stores are repleted.[24–27] Because the threshold effects of ID on development have not been established, it is prudent to assure that there are adequate stores during periods of growth and development. How can we assure good nutrition when, currently, secondary prevention is unlikely to be successful?

Much of the decline in the prevalence of IDA in recent years has been a result of primary preventative strategies, especially the fortification of formula and cereals with iron. One author has argued that daily supplementation should be continued through the second year of life.[28] Numerous studies worldwide have demonstrated the effectiveness of weekly preventative supplementation.[29–32] Given that most ID is not associated with anemia, these seem the most practical directions for future efforts. Screening toddlers for ID by Hb testing is inefficient. Prophylactic supplementation is likely to be more effective than attempting to identify and treat US children who are iron-deficient.

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POSTMARKETING SURVEILLANCE I

"The inadequacies of the postmarketing surveillance system (ie, Food and Drug Administration's MedWatch program with passive collection of spontaneous reports of adverse drug reactions) for ensuring safety are well known and include: reliance on voluntary reporting of adverse events by physicians and other health care professionals; poor quality of submitted reports, often with inadequate documentation and detail; underreporting of adverse outcomes with capture of only a small fraction of adverse events that actually occur; difficulty in calculating rates of adverse events because of incomplete numerator data on events, together with unreliable denominator data on exposure; limited ability for spontaneous reports to establish casual relationships; and difficulty in determining whether the adverse event resulted from the drug or the disease it was intended to treat. Yet the major problem with the current system for ensuring the safety of medications is that drug manufacturers are largely responsible for collecting, evaluating, and reporting data from postmarketing studies of their own products. This approach has many inherent problems. For instance, it appears that fewer than half of the postmarketing studies that manufacturers have made commitments to undertake as a condition of approval have been completed and many have not even been initiated."

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