Human and Ecological Risk Assessment, 12: 888–903, 2006
ISSN: 1080-7039 print / 1549-7680 online
DOI: 10.1080/10807030600826953

Considerations in Estimating Social and Economic Impacts of Immunotoxic Agents

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ABSTRACT

To make appropriate regulatory policy decisions, the potential social and economic impacts of the policy must first be established. For environmental and occupational agents, social and economic impacts are derived from animal toxicology and, when available, human studies that serve as the base for risk-benefit analysis (RBA). Because immune function is associated with resistance to infectious disease, developing RBA for data derived from immunotoxicology studies will require determining the changes in the frequency or severity of infectious disease resulting from an exposure. Fortunately, considerable information is readily available for identifying the frequency of infectious diseases in the general population and its social and economic impacts and to assist the risk assessor when conducting RBA for immunotoxicology endpoints. The following is a brief review describing some issues in using immunotoxicity data when conducting RBA. It presents an economic methodology to determine the economic impacts of infectious diseases to society, sources where these types of information are available, and an example using a specific infectious disease, otitis media.

Key Words: risk assessment, immunotoxicology, economic impact, risk factors, immune system disorders, cost of illness.

BACKGROUND

A large impetus for immunotoxicology research and testing is to identify and characterize potential human health risks so that such data can be incorporated into establishing regulatory or public health policies. The conceptual framework

Received 4 April 2005; revised manuscript accepted 27 August 2005.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute of Occupational Safety and Health.
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adopted by federal regulatory agencies, including the Occupational Safety and Health Administration (OSHA), Food and Drug Administration (FDA) and U.S. Environmental Protection Agency (USEPA), and the non-regulatory American Conference of Governmental Industrial Hygienists (ACGIH) to establish acceptable risk levels independent of the target organ/system, was developed by the National Research Council (NRC 1983), and is often referred to as the Redbook. This framework involves three phases including the collection of relevant research/testing data, conducting risk assessment and eventually conducting risk management. In the final phase, in addition to scientific evidence and risk estimates, various social, economic, statutory, and political factors are considered (Faustman and Omenn 2001). Whereas some statutes specify reliance on risk alone, others require a balance of risks and cost/benefits.

As summarized by O'Brien (2002), risk-benefit analysis (RBA) comprises a constellation of methods, drawn from many disciplines, and addresses the question of whether a risk is "acceptable." Whether this question is raised in the context of providing a clinical decision or public policy, the principles are the same: the analysis requires a comprehensive estimation and evaluation of risks and benefits, highlighting the trade-offs between the two that inform a policy decision. Such analysis also entails a careful quantification of the costs associated with a proposed program for reducing or avoiding risks (Wilson and Crouch 2001; O'Brien 2002). Within this process increasing attention has been placed on conducting and considering cost benefit analysis (CBA) and, most recently, cost-effectiveness analysis (CEA) (USEPA 2002, 2003; USOMB 1996, 2002, 2003).[1] This involves identifying the objective and subjective monetary costs, relative to similar benefits of the decision, including the magnitude and distribution of the impacts of the costs and benefits.

Data derived from the risk assessment process is a pivotal factor in accurately establishing RBA, often defined as CBA with the explicit incorporation of risk or uncertainty. Yet for the most part, immunotoxicologists conducting studies with the intention that such data may be used in the risk assessment/management process seldom consider study designs that can be used to aid in this analysis; epidemiologists continue to wrestle with uncertainty in exposure-outcome models; and economists, involved in risk management, may fail to communicate the types of information that would be most suitable for RBA.

IMMUNOTOXICOLOGY STUDY DESIGN ISSUES AND RBA

As with other toxicological endpoints, the interpretation of immunotoxicity data for use in risk assessment can be challenging. In addition to reoccurring issues such as interspecies extrapolation and transference from short-term, high-dose exposures to low-level, chronic exposure, there is a need to interpret changes in how immune

[1]Circular A-4 refines OMB's "best practices" document of 1996 (http://www.whitehouse.gov/omb/inforeg/riaguide.html), which was issued as a guidance in 2000; (http://www.whitehouse.gov/omb/memoranda/m00-08.pdf), and reaffirmed in 2001; (http://www.whitehouse.gov/omb/memoranda/m01-23.html). It replaces both the 1996 "best practices" and the 2000 "guidance for regulatory agencies." US Office of Management and Budget. 2003. Circular A-4; September 17, 2003. Available at http://www.whitehouse.gov/omb/inforeg/circular_a4.pdf

tests translate into potentially adverse health outcomes. Clinical or epidemiological data, when available, are often limited to white blood cell counts, immunophenotypic profiles or immunoglobulin levels and models are needed to extrapolate changes in these values to potential changes in disease incidence at various severity levels, as has been discussed for other endpoints (Buchanan *et al.* 2004; Dockins *et al.* 2004). Currently, systems biology approaches to derive accurate predictive description of disease (immunoinformatics) is in its infancy (Smith and Bolouri 2005). Because the most likely adverse clinical outcomes resulting from immunotoxic agents are presumed to be increased incidences and/or severity of infectious disease (Luster *et al.* 2005), when available, RBA should be conducted using data collected in humans where information describing changes in infectious disease incidence in the population of interest can be found.

Because many factors influence susceptibility to infectious disease, appropriate control populations will be needed to draw inferences. Such information can best be obtained for pharmaceuticals when well-controlled clinical studies are conducted. For most studies involving environmental or occupational agents, human data are derived primarily from observational or epidemiological studies and the methods used to collect such data are critical. For example, the incidence of community-acquired infections such as influenza is often collected solely from subject recall and is likely to be under-reported. Monitoring infectious disease incidence either by personal diaries or periodic interviews could improve data quality, especially if combined with better clinical testing as a simple blood test. Subject recall for the occurrence of opportunistic infections, such as *pneumocystis carinnii*, because of the rarity of these diseases, is likely to be more accurately recalled. However, such infections are relatively rare in the population and recognized as a result of profound immunosuppression. But, the frequency of infections resulting from latent virus reactivation, such as cold sores from Herpes simplex virus (HSV-1), can be measured relatively accurately provided there is confirmation of subject recall with coinciding elevation in serum viral antibody titers.

Due to the paucity of human data where immune tests and infectious disease incidences simultaneously are monitored in a population, most RBA will require the use of experimental animal studies where both immune and host resistance tests are conducted. Host resistance tests involve challenging groups of animals with an infectious agent or transplantable tumor cells at a challenge level sufficient to produce a low incidence in the control group (Germolec 2004). The infectivity rate in the control group is then compared to the rate obtained in groups treated with the test material. When host resistance assays are conducted in tandem with immune tests, it is possible to evaluate the resulting relationships. A number of studies have addressed the qualitative and quantitative relationships between commonly examined immune parameters and host resistance tests in experimental studies (Luster *et al.* 2005; Pruett *et al.* 2003; Selgrade 1999; Van Loveren *et al.* 1998). Such data collected from animal studies can be useful for RBA as it provides a basis for identifying the types and relative potency of infectious diseases that a population is at risk for developing.

DETERMINING SOCIAL AND ECONOMIC IMPACTS

Policy-makers are concerned with controlling and reducing risks to public health and often have strong pressures to produce acceptable solutions from limited

information. In a regulatory framework, risk standards provide a benchmark identifying when small changes in risk may define where the decision-maker might begin to address the costs to society of a potential intervention or program. In this setting, where the social perspective is being considered, risks are characterized by costs. When there is no standard, this task becomes more complex. When establishing a framework for immunotoxicity data to conduct RBA, it is important to develop a standard format and consistently organize disparate information on the impact of infectious diseases on the general population. The following is a brief discussion of a traditional approach used by economists to inform policy-makers of cost impacts.

When economists establish the social and economic impacts of adverse human health outcomes, they convert costs into monetary measures using, most often, the cost-of-illness (COI) method (Cooper and Rice 1976; Rice 1966; Rice *et al.* 1985). This cost methodology was reviewed by a task force of the U.S. Public Health Service (USPHS), which was convened in 1978–79, who were assigned to reduce methodological differences between COI studies (Hodgson and Meiners 1979, 1982). COI estimates provide an indicator or accounting of the economic changes that result from avoiding adverse health and are often used to measure the dollar value of benefits from a government program that might improve health outcomes, such as saving human lives or preventing diseases. They are unlike financial costs that just account for money used in health care. Economic costs additionally account for the resources that could be used elsewhere and that may not have a monetary value, although these are often difficult to capture. Note that in benefit-cost analysis, the concept measured is the difference between benefits and costs, an incremental picture of the value of an intervention or program. The COI method just portrays a part of that picture.

The willingness-to-pay (WTP) method, which values goods based on their worth to individuals, is sometimes used as an alternative to the COI method (Mishan 1971). There are two approaches within WTP used by economists. One approach estimates the value of risk reduction via questioning its reduced worth to individuals; that is, using a stated preference toward a hypothetical scenario, referred to as contingent valuation. The other approach uses the actual purchases of safety and health goods, thus revealing the choices made to reduce risks by an individual. Revealed preference is often used in cost-benefit studies. In both WTP approaches, individual values are aggregated to a society level. However, these social values are not considered to be a reliable measure of social welfare unless the additional or marginal value of income is the same for all income groups—a very unlikely "real-world" scenario (Freeman III 2003; Kenkel 1994; Kenkel *et al.* 1994). To reflect on WTP for an infectious disease consider the following example. If a disease is regulated and one in one thousand lives avoids the infection an average person is willing to pay $10 for this risk reduction, then each statistical case avoided is valued at $10,000. The regulated disease in a population of one million results in 1,000 fewer infected people and a $10 M (1 K × $10 K) savings to society. However, these are not all of the savings to society because the cost of implementing and enforcing the regulation is not considered.

There are no standardized processes to estimate COI dollars. However, COI studies include direct and indirect cost components associated with incurring an illness

and/or a premature death. There is general agreement on COI's two major components: medical costs and productivity losses. Sometimes these are the only two concepts that allow implementation of this approach. Both components are referred to as opportunity costs by economists. For example, if a person had not become ill, they would not have used the health care services or have lost productivity. Therefore, the money spent on their illness could be used elsewhere. This analysis does not include costs associated with disability, psychological effects, loss of well-being or changes in quality of life such as grief, pain, and changed social functioning.

Direct costs are the expenditures of health care goods and services, that is, the value of resources used in supplying health care, that would be spent elsewhere in the absence of the illness. It includes, for example, expenditures on health care professionals, hospitalizations, emergency room visits, drugs, and medical tests as well as non-medical costs such as insurance overhead related to that care.

Indirect costs are equated with lost productivity and are more likely a consequence of infectious disease. They account for the value of resources lost as a result of time absent from work or from other usual daily activity due to an illness or premature death. Indirect costs include lost earnings, lost fringe benefits, and lost household production such as the loss of household services and the value of caregiver's time that is taken away from household work or other outside employment to care for the ill-person. It would also include retraining and recruiting costs for businesses. Generally, these indirect costs reflect the cost of lost output to the economy because the social perspective is used, whereas direct costs reflect changes in consumption of health care and its related goods and services. Indirect cost estimates are complicated by the fact that if one had not become sick or died they would have continued to be productive so that indirect costs include lost potential productivity or future earnings.

Indirect costs are usually calculated by the "human capital" approach (Freeman III 2003; Mitchell and Carson 1989; Tolley *et al.* 1994). The human capital approach is best understood if an individual is thought to be like a capital good and, thus, investments that improve their health will have future returns, just as an investment in a piece of equipment does for a producer. To estimate indirect costs, national data on population estimates (USCB 2000), life expectancy (Arias 2004), labor participation rates, and earnings (USDOL 2005) are considered. Lost productivity is measured using lost earnings as a surrogate for the monetary value of lost labor, or an average market wage rate multiplied by a labor participation amount. The value of lost wages is estimated over the future and discounted to a present value based on the mortality or morbidity of the population being examined. When comparing the cost of different infectious diseases, the base or reference year, the discount rate (the rate used to value money's worth today compared to money's future value) and the inflation rate should be similar for each disease. For the most part, indirect costs derived from mortality data far outweigh those from morbidity because they cover the entire productive life of individuals. Because these amounts depend on the number of deaths or disabilities resulting from infectious disease, indirect costs usually exceed direct costs. Co-morbidities are usually not included as they are difficult to capture. However, both the severity and the possibility of recurrence of infectious disease should be considered as these will significantly affect the cost.

DEVELOPMENT OF COI ESTIMATES FOR INFECTIOUS DISEASES

COI estimates for infectious diseases are calculated from one of two perspectives: either prevalence-based or incidence-based. The use of each approach depends on the policy issues of concern and the illness. Both prevalence and incidence data are similar to those used in classical epidemiology. The incidence-based or lifetime cost perspective calculates the costs of the illness at its first diagnosis to some year in the future. This represents the total lifetime costs from onset in a particular year until death or cure and any lost productivity due to the illness occurring in later years, and not to just the time period in question (Hartunian *et al.* 1981). The prevalence-based approach, which is more commonly used, measures costs incurred during a particular period of time. The illness may have been initiated at a prior time but only costs for the year in question are considered. When productivity losses are determined for illnesses using this approach the discounted value of future earnings lost in that year due to the morbidity is calculated from the number of days of restricted activity-time adjusted for the probability that persons of a certain age and sex that incurred the illness in that year will survive to a certain age.

Productivity losses due to premature mortality represent the present discounted value of future earnings, which is established by determining the number of deaths in a particular year adjusted for life expectancy of those deaths by age and sex (Rice 1966; Rice *et al.* 1985). Because the dollar is used as a common measurement unit, one disease or the aggregation of groups of diseases can be presented to enable a policy-maker to prioritize and compare costs for different programs or interventions. Although the COI method provides a magnitude or indicator to which costs may be compared, some differences occur because data are unavailable, underreported, or overestimated. Some issues that should be considered when estimating COI for risk management purposes are listed in Table 1.

COI approaches are criticized for excluding the value of time of those who do not work such as children or retired individuals, and for not including the value of pain and suffering and lowered quality of life resulting from chronic infectious diseases.

Table 1. Measurement considerations in determining cost-of-illness.

- Resources that are used up to determine illness costs and related productivity
- Aggregation of different infectious diseases into a group vs. a single infectious disease
- Comparisons of costs across different illnesses
- Excludes the:
  - cost of pain and suffering
  - productivity of the young, elderly and unpaid worker
  - changes in quality of life
  - loss of well-being
- Productivity for non-wage earners and/or caregivers may be undervalued
- Disease definitions could vary even when using ICD codings
- Infectious disease episodes may be misreported
- Annual data may overlap two years (*e.g.*, flu season is October–April)
- Charges (insurance, medications, hospital services) if used for costs are overestimated
- Use of incidence vs. prevalence data
- Equating of work-loss days with days of illness

Controversy also arises over whether an individual's productivity is truly measured by their earnings. Because the COI method uses earnings to measure productivity, these losses may vary depending on education, sex, age, race, job skills, and other socioeconomic characteristics in the population. Although such variations could be accounted for, they are typically ignored in COI estimates for infectious disease. Some imputations can be done for caregivers who do not typically work outside the home. For example, the value of lost household services (Hartunian *et al.* 1981; Peskin 1984) might be imputed on the basis of expected earnings of service workers providing similar services as cleaners, cooks, babysitters, nurses, or maids. There are controversies over direct costs as well, and whether average spending on health care items truly reflects society's spending. Some argue that direct costs should reflect how income is distributed in society. The wealthier are able to spend more on health, purchase drugs, and use advanced technology. Low-income individuals, who may seek health care only after self-diagnoses and medications fail, might reflect only small amounts of health expenditures. Thus, an average might capture the greater spending of the more affluent but not the needs of the poor. Alternatively, costs of a pandemic of influenza might, for example, affect a large number of people at various income levels and reflect large costs.

Consistent estimating procedures are especially important when comparing economic costs of infectious disease. Health care costs do not have an official market price. They are often measured by hospital charges which may be over-inflated to meet insurance payouts and may not reflect the costs of the actual goods and services used. For many infectious diseases, there are differences in available data depending on the specific infectious agent, disease severity, or whether the disease is acute or chronic. Usually, primary diagnoses are used for specific illnesses, so that associated conditions or multiple diagnoses are ignored. This might be reflected in overstated direct costs and even overestimated productivity losses of a disease when economic costs are measured separately.

Estimating productivity losses also may be problematic. Wage data may include pension plans, health insurance, and flexible hours. It is also not clear whether a work-loss day, the usual value used to represent absenteeism, is always associated with illness. Collectors of surveillance data may differ in their definition of medical services. There is also a large amount of underreporting for many diseases, particularly common infectious diseases such as influenza where only about 20% of the illnesses are reported (NRC 1983). This is because the recording of influenza is dependent on whether the individual self-medicates or consults a doctor, that the physician recognizes the illness as viral, that blood is drawn and sent to a lab for testing, and that the lab recognizes the virus-borne pathogen is influenza and reports the case to the CDC. An example of this method will be illustrated in the last section using otitis media.

DATA SOURCES FOR DETERMINING THE COST OF INFECTIOUS DISEASE

Data on infectious disease can be obtained from population-based national health surveys providing information needed for a cost study at the society level. Commonly used population-based national health surveys employed in infectious disease research are shown in Table 2. Most of the national datasets classify morbidity and

Table 2. Some data sources for infectious disease incidences and costs.

Source	Link
Mortality counts	
Vital Statistics	http://www.cdc.gov/nchs/about/major/dvs/mortdata.htm
Morbidity counts	
NHANES	http://www.cdc.gov/nchs/nhanes.htm
NHIS	http://www.cdc.gov/nchs/nhis.htm
BRFSS	http://www.cdc.gov/brfss/
Morbidity costs	
HCUP	http://www.hcup-us.ahrq.gov/
MEPS	http://www.meps.ahrq.gov/

mortality by the International Classification of Disease (ICD) categories (NCHS 1991, 1993; WHO 1978, 1992). The purpose of ICD classifications is to enhance data comparability among countries. The ICDs are periodically revised. In the United States, the National Center for Health Statistics (NCHS) of the Centers for Disease Contol and Prevention (CDC) serves as the World Health Organization's (WHO's) collaborating center and is responsible for the coordination of these activities. At the time of this writing, the ICD Ninth Revision, Clinical Modification (ICD-9-CM) (NCHS 1991) is the official system of assigning codes to morbidity data in the United States. The ICD-9-CM is used to classify diagnoses and reasons for visits in all health care settings such as for inpatient and outpatient records, doctors' offices, and official government surveys and is very detailed. Infectious diseases are coded in chapter 1 "Infectious and Parasitic Disease (001-139)" of the ICD-9-CM manual. For example, salmonella is coded 003, acute polio 045, chickenpox 052, viral hepatitis 070, acute respiratory infection 460–466, and influenza and pneumonia 480–487. An example of a classification of infectious disease mortality by ICD-9s for a research study is shown in Table 3 (Pinner *et al.* 1996). For other examples of infectious disease classifications see Armstrong and Pinner (1999) and Simonsen *et al.* (1998). In the United States, the tenth version (ICD-10-CM) (NCHS 1993)[2] is in the process of revision, but ICD-10 has been used to code and classify mortality data from death certificates since January 1999 (WHO 1992). An online version of the ICD-10 can be found at the WHO website (WHO 1992). A crossover file showing the relationship from the last version of ICD to the subsequent one is usually provided. Also, NCHS produces conversion tables for earlier versions of the ICDs.

Mortality data can be found in the National Vital Statistics System at CDC/NCHS (Kochanek and Smith 2004). A general overview of the surveys and data collection systems conducted by CDC/NCHS, can be found at http://www.cdc.gov/nchs/express.htm.

Morbidity data can be obtained from many sources that are generalized for the U.S. population. Count resources include the National Health and Nutrition Examination Survey (NHANES) (NCHS 2005a) and the National Health Interview Survey (NHIS) (NCHS 2005b), both sponsored by the CDC/NCHS; and the

[2]ICD-10-CM was sent out for public comment in June 2003 and should be available soon.

Table 3. Infectious disease groups and related international classification of disease and related health conditions, ninth revision (ICD-9) codes.

Selected Infectious Disease Group	ICD-9 Codes
Tuberculosis	010.0–018.9, 137.0–137.4
Bacterial meningitis	027.0, 036–036.9, 320–321.3, 321.8
Septicemia	038–038.9
Human immunodeficiency virus/ acquired immunodeficiency syndrome	042–044, 279.1
Hepatobiliary disease	070.0–070.9, 576.1
Selected perinatal infections	090.0–090.9, 770.0, 771.0–771.8
Mycoses	110.0–118.0
Infections of the heart	391–391.9, 393, 394.1, 395.0–395.2, 397.1, 397.9, 398–398.9, 421, 422.0, 424.9
Selected respiratory tract infections	460.0–466.1, 475, 480–487.8, 510.0–510.9, 513.0–513.1
Selected gastrointestinal tract infections (appendicitis, peritonitis, abscess of the intestines)	540–542, 566, 567.0–567.2, 569.5
Infections of the kidney and urinary tract	590.0–590.9, 599.0

Source: Pinner *et al.* (1996).

Behavioral Risk Factor Surveillance System (BRFSS) (CDC and NCCDPHP 2004) of the CDC/National Center for Chronic Disease Prevention and Health Promotion. Additional sites listed at CDC/NCHS focus on certain components of morbidity such as outpatient visits in the National Ambulatory Medical Care Survey (NAMCS) (NCHS 2004b) and hospitalizations in the National Hospital Discharge Survey (NHDS) (NCHS and HCSB 2005). Another federal agency, the Agency for Healthcare Research and Quality (AHRQ) collects cost data in its Healthcare Cost and Use Project (HCUP) (AHRQ 2005) and its Medical Expenditure Panel Survey (MEPS) (AHRQ 2004). Influenza surveillance is conducted at the CDC through an agreement with the WHO. The seven components of their surveillance system and an overview of their methods and weekly surveillance reports for the U.S. influenza season can be found online (USDHHS and CDC 2005).

Another resource, which is part of CDC's Emerging Infections Program, is FoodNet (CDC 2005). This is a food-borne disease surveillance network that conducts surveillance for laboratory-confirmed cases of seven bacterial and two parasitic organisms. Each surveillance system and survey has unique issues related to its purpose, sample design, implementation and response rates that can influence estimates. Finally, the literature can be reviewed for recent estimates and hypotheses can be generated from disease distributions using Monte Carlo (MC) simulations (Robert and Cassela 1999); also see Meltzer *et al.* (1999) for an example of MC applied to pandemic influenza. Again, these databases have uncertainties or biases in their estimates and awareness should be given to the concepts and methods that were used to capture the information collected.

Sample cost data from a recent NIH study on COI for different diseases are presented in Table 4 (USDHHS and NIH 2000). The authors of this study warn users not to use this information for comparing diseases across categories because of the

Table 4. Some cost of illness estimates.*

Illness	Total cost	Direct cost	Indirect cost
Pneumonia and Influenza	$25.6b	$18.6b	$7.0b
Otitis media	$5.0b	$2.9b	$2.1b
Respiratory Distress Syndrome	$4.1b	$3.2b	$0.9b
Neonatal Respiratory Distress Syndrome	$1.1b	$0.7b	$0.4b
Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome	$28.9b	$13.4b	$15.5b
Chronic Obstructive Pulmonary Diseases	$37.3b	$21.6b	$16.2b
Septicemia	$7.2b	$4.9b	$2.3b
Tuberculosis	N/A	$0.7b	N/A

* Source for individual diseases USDHHS and NIH (2000).

many conceptual and methodological issues that occur in gathering disease information. These include the disease definition, the cost components measured, the discount rate, and the reference year. They believe a range of uncertainty should be attached to each cost estimate because the surveys from where the data are obtained also contain implicit sampling errors and significant variations in methods and data captured.

DEATH RATES IN THE UNITED STATES FROM INFECTIOUS DISEASES

In 2002, life expectancy in the United States reached a new high of 77.3 years with deaths still having the most costly impact on society. The 15 leading causes of death in 2002 accounted for 83.3 percent of all deaths in the United States. (Kochanek *et al.* 2004). Deaths in categories related to chronic lower respiratory infections were ranked 4th at 5.1%; 7th at 2.7% for influenza and pneumonia; and 10th at 1.4% for septicemia. The age-adjusted death rates, ICD-10 classifications in parenthesis, for these four illnesses were 43.5 (J40-J47), 22.6 (J10-J18), 11.7 (A40-A41), and 6.1 (J69) per 100,000 standard population, respectively (WHO 1992). Although human immunodeficiency virus (HIV) is not on this list, it is still considered to be a major public health problem. In 2002, 0.5% of total deaths resulted from acquired immunodeficiency syndrome (AIDS) and the age-adjusted death rate was 4.9 per 100,000. Recently, health care expenditures were tracked for medical conditions from 1987 to 2000 and were found to increase from $429 billion to $628 billion. Thorpe *et al.* (2004) additionally found that 15 diseases accounted for more than half of that increase with pneumonia ranking 12th and other infectious diseases ranking 13th.

ILLUSTRATION OF COI APPROACH FOR OTITIS MEDIA

To illustrate the COI approach, we used data from an AHRQ study that provided estimates for otitis media (OM) in the year 2001 for children under 4, the group most susceptible to infection (Miller and Carroll 2005). The ICD-9-CM codes for OM are 381 and 382. Note that the example is based on many assumptions for both

dollars and numbers that have not been reported in published statistics but have been chosen at the authors' discretion. The population of children 4 and under was estimated to be approximately 20 million in 2001 and about 6 million children were reported to have OM. As with other infectious diseases, many factors will influence the actual cost estimate including variability in medical care and prescription use. Because there are no isolates for OM, clinical diagnosis is subjective and the illness may be over-diagnosed. An antibiotic is commonly prescribed but sometimes the infection is asymptomatic and resolves naturally. The clinical manifestations of OM include pain, fever, and changes in activity levels that are usually evident in the first 3 days of the infection with most of the illness being resolved by the 10th day. Usually the antibiotic treatment is repeated if the infection is extreme or unresolved. The infection may reoccur in 1 to 3 months, and after 4 occurrences is classified as a chronic OM case. If the infection is not resolved after four or more repeated episodes that utilize stronger antibiotic medication, an ear, nose, and throat specialist is usually recommended, and a surgical procedure, myringotomy or tympanostomy tube insertion, follows.

The Miller *et al.* (2005) study examined trends in antibiotic use through prescriptions and changes in emergency room and doctor visits and changes in antibiotic use resulting from these visits. These numbers, although useful, are not the actual reported numbers of visits relating prescription use, office visits, and antibiotic use needed for a cost estimate for OM itself but are somewhat related because antibiotics are usually the first clinical recommendation for this illness. There were about 5 million children with OM that received antibiotics in 2001, with each receiving an average of 2.1 prescriptions. Note that this does not include over-the-counter medicines as ibuprofen and acetaminophen. It does not differentiate between medicines prescribed but not purchased or acquired but not used. Death, the most expensive component in a COI study, is rare for OM and, if death does occur for a child, OM is usually a secondary diagnosis. Medical costs can be determined from information on medical care, prescription use, and so on. Productivity losses are not clear for children. There are losses for the parent or care-giver. A typical COI estimate tends to ignore the value of children because they do not produce output for society and do not have opportunity costs even though children do have value. During an OM illness, care-givers as the parent, babysitter, or other paid caregiver would have opportunity costs for their time and some productivity losses. There is little evidence that person-to-person transmission of OM occurs although it seems that transmission does occur in group settings such as day-care centers or other communal or educational environments. Of course, illness severity and individual susceptibility are quite variable for OM.

Direct costs include doctor visits and medications. Some hospitalization may occur with children in severe distress, although these are usually rare. Medications would include prescription drugs and over-the-counter (OTC) medications. Analgesics would be given for fever, pain, and irritability such as ibuprofen and acetaminophen. Sometimes OTC medicine is continued after the episode to prevent a recurrence. The most common prescribed medication is amoxicillin. A more powerful antibiotic as zithromax is used for more severe cases. If this disease is untreated, permanent hearing loss and developmental disabilities could occur and affect future productivity.

Table 5. Estimates of direct and indirect costs of OM per case.

	Direct costs	Indirect costs	Total costs
Mild OM	$65	$173	$238
Acute OM	$140	$452	$592
Chronic OM	$1310	$904	$2214

A case study by Carabin *et al.* (1999) included 512 Canadian children. Of these 191 were 6 to 23 months of age and 321 were 2 to 5 years of age. In that study, 29 children or 5.7% had mild OM, 415 or 81.1% had moderate OM, and 68 or 13.3% had severe OM. Applying these approximations to the 2001 estimates of 6 million children 4 and under with OM would result in more than 300,000 children with mild OM; 4.9 million children with moderate OM, and 800,000 children with severe OM. A mild case would entail one doctor's visit plus one prescription with no renewal for amoxicillin, and some OTC medication at $5 totaling $65. A mild case of OM would provide uncertainty to a parent. They would probably make one visit to a physician and may stay home with the child for the rest of the day losing one day from work. We assumed that the travel costs to and from the doctor are about $10, the travel to and from a pharmacy is about $3 each and the day away from work would cost approximately $20 an hour. This would total $173. Approximately $140 of medical costs is estimated for each moderate or acute OM case assuming each case receives 2 prescriptions, each with one renewal, for a common inexpensive drug such as amoxicillin at $10 each, at least 3 visits to a medical professional—initial visit with a no charge follow-up visit, and a return visit at $50. A severe case or chronic OM would include 3 consecutive office visits, each with a follow-up and a 2-course regimen of a stronger antibiotic such as zithromax at $35 each, a specialist visit at $150, and a tympanostomy tube insertion as an out-patient for $750, and one return checkup visit at $50, totaling $1,310. A moderate case might require 2.5 days away from work for 2 physician visits with 2 follow-ups and 4 trips to a pharmacy, for doctor visits and monitoring the child's well-being totaling $452. This chronic case would entail 5 days away from work for doctor visits, out-patient surgery, and for monitoring the child's well-being plus 8 trips to a pharmacy, totaling $904. Cost data per case are summarized in Table 5 and total COI to society for OM are summarized in Table 6. These results are comparable to those found by Gates (1996) using similar assumptions.

Table 6. Societal estimates of Otitis media ($billions).

	Number of cases (millions)	Direct costs ($billion)	Indirect costs ($billion)	Total costs ($billion)
Mild OM	0.3	$0.019	$0.052	$0.071
Acute OM	4.9	$0.686	$2.215	$2.901
Chronic OM	0.8	$1.048	$0.723	$1.771
Total	6.1	$1.753	$2.990	$4.773

SUMMARY

Increasing efforts have been made to incorporate immunotoxicity data derived from experimental or epidemiological studies into the risk assessment process. An example has been presented of an economic analysis and data sources that can help this process. Currently, the main challenge in developing RBA models for immunotoxicology remains the inability to establish precise quantitative relationships between changes in commonly used immune tests and the increased frequency of infectious disease. Until this can be accomplished, it will be important to design clinical and epidemiological studies that will capture both these endpoints. The information described earlier suggests the types of epidemiological and experimental animal study designs that lend themselves to RBA. It summarizes the wealth of population data, and the social and economic impacts derived from COI studies that can be useful in developing a framework for conducting such analysis.

ACKNOWLEDGMENTS

This review was prepared in conjunction with the Immunotoxicology Workgroup sponsored by the USEPA, Office of Research and Development (ORD), National Center for Environmental Assessment (NCEA) and Health Effects Research Laboratories (HEERL); USEPA/Office of Children's Health Protection (OCHP); USEPA/Office of Pesticide Protection and Toxic Substances (OPPTS); the National Institutes of Health (NIH), National Institute of Environmental Health Sciences (NIEHS); and the National Institute for Occupational Safety and Health (NIOSH), Health Effects Laboratory Division (HELD).

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