An OAHPP/ ICES Report

Ontario Burden of **INFECTIOUS DISEASE** Study

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ONTARIO BURDEN OF INFECTIOUS DISEASE STUDY

OAHPP/ICES Report

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CONTENTS

Executive Summary

Background

Over the past decade, infectious diseases have regained prominence in Ontario, with outbreaks of *E. coli* O157:H7, West Nile virus, severe acute respiratory syndrome (SARS) and pandemic H1N1 influenza. The Ontario Burden of Infectious Disease Study (ONBOIDS) provides a current assessment of the mortality and morbidity of infectious disease in Ontario. The study's objectives were to: determine the relative contributions of select infectious diseases to the overall burden of infectious diseases in Ontario; inform priority setting, planning and decision-making; establish a baseline for future evaluations of public health interventions; and identify strengths and weaknesses of existing infectious disease data in Ontario.

The study

ONBOIDS built on previous international and Canadian work. A composite health gap measure—health-adjusted life years (HALYs)—was used to assess disease burden. HALYs allow for the simultaneous description of both premature mortality and the reduced functioning or suboptimal state of health associated with diseases or injuries (i.e., morbidity). HALYs quantify the amount of "healthy" life lost by estimating the difference between actual population health and a specified norm or goal.

Disease burden was estimated by pathogen (e.g., *Streptococcus pneumoniae*) and by syndrome (e.g., pneumonia); 51 distinct infectious pathogens and 16 syndromes were considered. We focused on those infections that were severe enough to require health care or which were reportable; for selected pathogens, we adjusted for underdiagnosis and underreporting. To reduce some of the anticipated year-to-year variability arising from the dynamic nature of infectious diseases, we estimated annual disease incidence and mortality by calculating three-year averages from the latest data available. Deaths that occurred during 2003–2005 were extracted from Ontario vital statistics data. Disease incidence was estimated for 2005–2007 by compiling Ontario reportable disease data, health care utilization data and cancer registry data, and supplementing with local modeling studies and national and international epidemiologic studies. Etiologic agent distributions for non-specific syndromes and average durations of disease courses were determined from epidemiologic studies and expert opinion. Severity weights for the various health states were generated using the Classification and Measurement System of Functional Health (CLAMES) instrument developed by Statistics Canada.

Findings

- Each year in Ontario, there are over 7,000,000 infectious disease episodes and nearly 4,900 deaths from infectious diseases.
- Infectious diseases accounted for 82,881 HALYs, comprising 68,213 years of life lost due to premature mortality and 14,668 year-equivalents of reduced functioning; more than 80% of the disease burden associated with infectious diseases is from premature mortality rather than from disease-associated morbidity.
- The 10 most burdensome infectious agents were: hepatitis C virus (HCV), *Streptococcus pneumoniae*, human papillomavirus (HPV), hepatitis B virus (HBV), *Escherichia coli*, human immunodeficiency virus (HIV/AIDS), *Staphylococcus aureus*, influenza, *Clostridium difficile* and rhinovirus; nearly 50% of the total burden of infectious diseases could be attributed to the top five pathogens.
- Among selected infectious syndromes, the five most burdensome were pneumonia, septicaemia, urinary tract infections, acute bronchitis and endocarditis.
- There was a dramatic range in the severity of infections—from the common cold to terminal AIDS—and duration of illness—from days (e.g., for cystitis and upper respiratory tract infections) to decades (e.g., for HIV and the sequelae of bacterial meningitis).
- A large proportion of the burden of illness could be attributed to a small number of pathogens and syndromes for which highly effective targeted interventions (e.g., pneumococcal, HBV and HPV vaccines) and non-specific interventions (e.g., hand washing, male and female condoms) already exist, so the future burden of some of these infectious agents and syndromes may be dramatically reduced with greater uptake of available interventions.
- The mortality and morbidity associated with illnesses that can be prevented by childhood vaccination (e.g., measles, mumps, rubella, tetanus, polio and diphtheria) have been largely eliminated as a result of the success of routine childhood vaccination programs. These remain priorities to ensure that control is sustained.
- A significant burden associated with infections is caused by pathogens that constitute the human body's normal microbiological flora (e.g., *E. coli*, *S. aureus*). These infections often take place in health care settings. Addressing this burden will require interventions that minimize transmission of these pathogens to normally sterile body sites and emphasize the ongoing need to strengthen infection prevention programs in health care settings.

- Although the overall burden was similar between males and females, marked differences in sex-specific burden were noted for certain pathogens (HCV, HBV, HPV and HIV/AIDS) and syndromes (e.g., urinary tract infections).
- The burden of infectious diseases often correlates poorly with public perception, media attention and resource allocation; many of the pathogens ranked among the top 20 receive little recognition as significant contributors to disease burden in the population.
- The total burden of infectious diseases was equivalent to roughly 25% of the burden of all cancers (estimated in a previous Canadian study).*
- The ranking of infectious diseases was similar to that reported in a European pilot study** that assessed the burden of only seven pathogens, and the magnitude of the burden was comparable to the findings of a previous Australian study^ for some infectious diseases (e.g., HIV/AIDS, chlamydia) but not others (e.g., HCV, tuberculosis). This provides some validation of our methods.

Strengths and weaknesses

The study is a thorough examination of the burden of infectious diseases. Strengths of the study include the expansion of the use of the pathogen-based approach; the comprehensiveness of infectious diseases included; the inclusion of a broader range of health states/sequelae of infectious diseases; and the use of linkable health care utilization data. To our knowledge, this represents the most thorough examination of the burden of infectious diseases to date, worldwide.

In such an ambitious undertaking there are inevitably limitations to both the data available and the methods applied. Identification of such limitations was indeed an objective of the study. Our approach had similar limitations to those of other burden of disease studies. These included: the static nature of the burden of disease methodology and its implications for dynamic processes, such as infectious diseases; suboptimal data quality and availability; the scope of the study being restricted to the health burden and not economic or psychosocial impacts; questions related to the generalizeability of the etiologic agent distributions; the exclusion of certain important infectious agents, syndromes and health states; and the burden of undiagnosed and unreported cases.

Interpretation and recommendations

- Further work is required to improve the timeliness of data access and the quality of information available. A top priority should be to improve the data infrastructure required for surveillance, high-quality research and program evaluation by expanding the linkage of data sources already in existence.
- While the prevention of some infectious diseases will require the development of novel interventions, much of Ontario's infectious disease burden could be reduced through better implementation of existing interventions.
- The estimated burden of a disease is only one of a multitude of considerations necessary for setting priorities for future action. A critical evaluation of the effectiveness of available interventions, as well as economic, political and ethical considerations, are also important components of priority setting.
- Efforts such as ONBOIDS serve to inform decision-making, identify areas of future research and action, and highlight gaps in data availability and quality. These findings can assist planners, decision-makers, practitioners and researchers in their efforts to improve the health of Ontario's population.

* Public Health Agency of Canada. Population Health Impact of Disease in Canada (PHI). Accessed on September 13, 2010 at http://www.phac-aspc.gc.ca/phi-isp/index-eng.php.

** van Lier EA, Havelaar AH, Nanda A. The burden of infectious diseases in Europe: a pilot study. Euro Surveill 2007; 12(12):E3–4.

^ Mathers C, Vos T, Stevenson C. The Burden of Disease and Injury in Australia. Canberra, Australia: Australian Institute of Health and Welfare; 1999. Accessed on September 13, 2010 at http://www.aihw.gov.au/publications/phe/bdia/bdia.pdf.

Introduction

In the face of limited health resources, the increasing importance of evidence-based priority setting, health program evaluation, and economic evaluation has led to a demand for enhanced knowledge about the relative contributions of specific diseases and injuries to the loss of healthy life.[1]

Several methods to quantify population-level disease burden have been proposed. The Global Burden of Disease (GBD) method was first proposed by Dean T. Jamison at the World Bank in the *1993 World Development Report*.[2] Subsequently, the Harvard School of Public Health was contracted to construct first estimates, and the methodology was used by the World Health Organization (WHO) to assess the health of populations; similar approaches have been taken to assess regional, state level, or national burden of disease (e.g., European Union, Australia).[3,4] Building on this work, Statistics Canada and the Public Health Agency of Canada collaborated on the Population Health Impact of Disease in Canada (PHI) project.[5] These types of approaches have never been used to assess disease burden in Ontario. Since the mission of the Ontario Agency for Health Protection and Promotion (OAHPP) is "to support health care providers, the public health system and partner Ministries in making informed decisions and taking informed action to improve the health and security of all Ontarians through the transparent and timely provision of credible scientific advice and practical tools," assessing the provincial burden of diseases and injuries is consistent with OAHPP's mandate.

The Ontario Burden of Disease Study (ONBODS) is a three-year project designed to provide three comprehensive reports on the burden of disease for Ontario. Because OAHPP was created partially in response to the severe acute respiratory syndrome (SARS) outbreak of 2003, it seemed logical to start a burden of disease study with a focused assessment of infectious diseases, resulting in the Ontario Burden of Infectious Disease Study (ONBOIDS). Unlike certain chronic health conditions (e.g., cancer, diabetes), very little research has previously been conducted in Ontario or Canada to quantify the burden of infectious disease. A study dedicated to infectious disease would fill that knowledge gap and provide an in-depth picture of a larger number of infectious agents than has been typically included in burden of disease studies. Future reports will examine the burden of mental illness and addictions, and the burden associated with risk factors for chronic diseases.

The objectives of ONBOIDS are to:

1. Determine the relative contributions of various infectious diseases to the overall burden of infectious diseases in Ontario.
2. Inform priority setting, planning and decision-making.
3. Establish a baseline for future evaluations of public health interventions.
4. Identify strengths and weaknesses of existing data on infectious diseases in Ontario, and define areas requiring improvement.

There are a number of limitations to burden of disease studies, which is why identifying strengths and weaknesses was made an objective of the study. An explicit health economic component has not been included in the analysis. Furthermore, while we were for the most part able to assess the disease burden associated with health care utilization, we were generally not able to include the economic, societal and individual impacts of many mild but commonly occurring infections that do not come to the attention of clinical or public health services. We acknowledge that these are of great economic significance and deserve consideration at a later stage.

We also did not include an evaluation of the full impact of infectious disease outbreaks. These, as seen with SARS and the 2009 H1N1 pandemic, may have much broader economic and societal impacts than their effect on the health of a population. The methods used in this study do not permit such an assessment to be done. Novel methods are needed to comprehensively assess the health and economic burden of outbreaks of infectious diseases.

Finally, this report does not include an assessment of the success of interventions. For example, we do not present the burden of disease prevented by interventions such as vaccination programs, early antibiotic treatment for invasive bacterial disease and hospital infection control. These are vital public health programs. In general, vaccine-preventable diseases have very low remaining burden of illness precisely because the programs are so successful. Furthermore, several of the infections which we identified as having significant burden are also those for which new vaccines are under development. An important complementary study to carry out would be an investigation of the number of lives saved and morbidity prevented through various intervention strategies (e.g., vaccination). The findings of this report support continued investments in all these areas and should in no way be interpreted as meaning that they deserve any less attention in the future.

Overall Methods

The methodology for ONBOIDS was adapted from the GBD and PHI studies.[1,5,6] In order to measure and compare the burdens associated with different diseases it is necessary to quantify the burden for each disease using an appropriate summary measure of population health.

We used the health-adjusted life year (HALY). The HALY is a composite health gap measure that allows for the simultaneous description of both mortality and morbidity by incorporating deaths occurring before a pre-specified life expectancy (premature mortality) and the reduced functioning or suboptimal state of health associated with diseases or injuries. HALYs quantify the amount of "healthy" life lost by estimating the difference between actual population health and some specified norm or goal. HALYs are an umbrella term for a family of measures, including disability-adjusted life years (DALYs) and quality-adjusted life years (QALYs).[7]

A scientific advisory committee composed of investigators with the appropriate expertise (e.g., infectious diseases specialists, public health physicians, epidemiologists) oversaw the process. This committee identified the disease groups and diseases/agents to include in the study. Members from this group and other experts formed smaller disease group subcommittees to identify health states and appropriate data sources for each disease. They also reviewed the data collected to ensure plausibility and clinical accuracy. The approach was driven, at least in part, by the availability of data; gaps were identified in order to make recommendations on future needs for improved data access and quality.

2.1 OUTCOME MEASURES

Years of life lost due to premature mortality (YLL)

YLL measures the years of potential life lost due to premature mortality (Equation 2.1). YLL is calculated for each age group for each infectious agent/disease. To get the YLL for each age group and for each agent, the number of deaths in an age group due to a particular cause is multiplied by L, the standard loss function. L is the number of years of life lost due to premature mortality in each age group. The YLL for each age group is summed to get the YLL for an agent. Deaths that were ill-defined were proportionally redistributed to relevant causes.

Equation 2.1:

$$YLL_{c,a,s} = N_{c,a,s} * L_{a,s}$$

Where:

$N_{c,a,s}$	=	number of deaths due to cause (c) for a given age group (a) and sex (s)
$L_{a,s}$	=	standard loss function in years (number of years of life lost due to premature mortality for the age and sex stratum)

Year-equivalents of reduced functioning (YERF)

YERF measures the years of healthy life lost due to reduced functioning as a result of a disease or condition (Equation 2.2). The calculation of YERF for each infectious disease required the following steps:

1. A detailed description of the natural history of each disease and its associated health states was determined. Each disease could have multiple health states which outline the possible stages in the progression of the disease.
2. The incidence for each health state of each disease was estimated. Information on health state incidence was collected from Ontario data when available and/or epidemiologic studies, or was approximated using overall disease incidence and distribution of the disease by health state (disaggregated by age group and sex whenever possible).
3. The duration of each health state was determined. We assumed the duration was uniform across age and sex because age- and sex-specific estimates were not available.
4. The severity weight associated with each health state, also assumed to be uniform across age and sex, was determined by an expert medical panel using the Classification and Measurement System of Functional Health (CLAMES) methodology.[8] (See Severity Weights and Appendix A for further details).
5. The YERF for each health state (for each age group and sex) were calculated by multiplying the incidence by the severity weight and duration. The YERF for each health state were then calculated by adding the YERF for age groups and sexes within the health state.
6. The YERF for each disease were ascertained by summing the YERF for each health state associated with the disease.

The process of calculating YERF required information from multiple data sources. The incidence of disease and health states was collected from various sources, such as reportable disease and health care utilization data, as available and appropriate. Epidemiologic studies were most often used to ascertain estimates of health state duration and the distribution of disease by health state.

Equation 2.2:

$$YERF_{c,h,a,s} = I_{c,h,a,s} * D_{c,h} * SW_{c,h}$$

Where:

$I_{c,h,a,s}$	=	incident cases by cause (c), health state (h), age (a), and sex (s)
$D_{c,h}$	=	average duration of health state
$SW_{c,h}$	=	severity weight associated with health state

Health-adjusted life years (HALYs)

The HALYs for each disease were calculated by adding the YLL and YERF for the disease (Equation 2.3),

Equation 2.3:

$$HALY = YLL + YERF$$

In theory, the HALY measures future healthy years of life lost due to each incident case of disease or injury. It is thus an incidence-based measure rather than a prevalence-based measure.

Social value choices

The calculation of HALYs requires several distinct social value choices. There were four main social value choices made by the ONBOIDS investigators.

1. Life expectancy

Life expectancy (LE) is the number of years a person could be expected to live from a given age. The calculation of YLL requires the definition of a standard loss function (L) that represents the LE for that age group (See Equation 2.1). The standard loss function, and subsequent calculation of YLL, will vary depending on the LE used.

In the GBD study, the same predefined LE (by age group and sex) was used for all countries. This was based on the highest attainable LE using the Coale and Demeny West level 26 model life table.[9, 10] For females, the highest LE at birth was 82.5 years (the life expectancy for females in Japan). For males, LE at birth was set at 80 years based on the presumed biological difference between the two sexes (2.5 years).

In this study, we used the LE for the Ontario population (82.0 years for females and 77.4 years for males) to take into account the local demographic profile,[11] although we appreciate that by not using the LE from the GBD study our results may be less comparable to other burden of disease studies worldwide.

2. Age weighting

Due to changing levels of dependency and productivity throughout the life course, a year of life lost at age 30 may be valued more highly than a year of life lost at age 75. In the GBD study, non-uniform age weights were used to give the highest weight to years lost in young adulthood.[1] This decision was based on economic value, as young adults are considered more productive and necessary to the economy. However, the use of age weights to adjust the calculation of DALYs is controversial. Age weighting is highly debated as it violates principles of societal equity.[12] Furthermore, the quantitative methodology used to implement age weights in the calculation of DALYs has been called into question.[13] Finally, to our knowledge there is insufficient evidence that Canadians value a year of life lived in a particular age group more than others. For these reasons, age weighting was not used in our analysis.

3. Discounting

Discounting means that future life years are assigned less value than those lived today. This is based on the economic concept that one prefers benefits now rather than in the future.[14] The GBD study discounted future life years at a rate of 3%. Using this discount rate, a year of healthy life lived in 10 years time is worth 24 percent less than a year of healthy life lived in the present.[15]

As with age weighting, there is controversy regarding the application of discounting to future health effects. It has been argued that life does not lose value to society if it is in the future rather than the present[16] and that life cannot be valued in strictly monetary terms. Thus, applying economic theories such as "opportunity costs" may not be appropriate.[13] It has also been argued that discounting biases health policy against preventive health programs (e.g., vaccination, smoking cessation), which tend to have longer term benefits, in favour of acute therapeutic care which has immediate benefits. Finally, it is also unknown if Canadians prefer health benefits in the present as opposed to in the future. Due to this controversy, the current analysis was conducted without discounting.

4. Severity weights

Severity weights (or health state valuations) quantify societal preferences for different health states. These weights do not represent the lived experience of any health state, or imply any societal value of the person in a health state. Rather, they quantify societal preferences for health states in relation to the societal "ideal" of optimal health. The weights for HALY calculation are expressed on a scale from zero to one, with zero representing a state of optimal health and one representing a state equivalent to death. The GBD study developed disability weights using responses from individuals in 10 different countries. However, there was incomplete alignment between diseases and health states evaluated in the GBD study and those included in ONBOIDS—ONBOIDS evaluated a far more extensive number of infectious diseases. Therefore, a set of Ontario-specific severity weights was developed.

The CLAMES methodology was previously developed as part of the PHI study for generating preference scores for the Canadian population.[8] CLAMES used the Standard Gamble (SG) methodology with predominantly lay panels to capture "society's preferences" more accurately than previous studies. A drawback was that classifications (the combination of scores for 11 distinct attributes) were previously

developed for only a relatively limited number of diseases (including 24 infectious diseases). Consequently, ONBOIDS researchers assembled a panel of health professionals to develop a classification for each health state under investigation using the CLAMES system. The system provides a preference weight for any potential classification. A severity weight is obtained by subtracting the CLAMES preference weight from 1.0. A more detailed description of the methods used to generate the severity weights can be found in Appendix A.

Comparing HALYs, DALYs, and QALYs

The concept of HALYs and the similarities and differences between DALYs and QALYs have been reviewed in detail previously.[7] The most salient differences between DALYs and QALYs are:

- QALYs have been used by health economists since the 1960s predominantly for evaluating interventions in clinical settings,[17] whereas DALYs were developed in the 1990s for measuring and comparing disease burden in populations.[2]
- QALYs can be thought of as "a good" to be maximized, whereas DALYs, as a health gap measure, can be thought of as "a bad" to be minimized. The term "QALYs lost" can be used in a similar way that DALYs are generally used.
- Age weighting is generally applied to DALYs and not to QALYs. As described above, age weighting applies more weight to the disease burden afflicting working-age adults. But the use of age weighting is controversial and the ONBOIDS advisory committee chose not to apply age weighting in ONBOIDS.
- The GBD study incorporated discounting future time at a rate of 3% for DALYs, whereas discounting is not necessarily included in QALY calculations. The use of discounting will reduce the apparent burden of chronic conditions relative to acute conditions. However, as stated previously, we did not discount in this study.
- DALYs generally use disability weights (0 = perfect health and 1 = death) that often rely on expert opinion to place conditions on a continuum of disability, whereas QALYs use utility weights (0 = death and 1 = perfect health) that are generated through preference exercises using techniques such as the standard gamble. Use of the CLAMES instrument effectively produces utility weights, which we converted into severity weights by subtracting from 1.0.
- Finally, DALYs are frequently separated into the mortality (YLL) and morbidity (years of life lived with disability, or YLD) components, whereas QALYs generally are not.

Since the objective of ONBOIDS was to estimate the burden of infectious diseases at the population level, and since the available data facilitated the division of the burden into the mortality and morbidity components, we considered using DALYs rather than QALYs as the outcome measure. However, because the advisory committee chose not to use age-weighting, discounting or the standard GBD life expectancy, and also supported the use of the CLAMES instrument rather than incorporate disability weights from the GBD and other DALY-based studies, we did not feel it was appropriate to label our outcome measure a DALY. As our desired outcome measure had attributes of both DALYs and QALYs but was technically neither, we used the more generic HALY as our outcome measure. In addition, by using HALYs we maintain consistency with the PHI study which was conducted in Canada.[5]

To assess the impact of using HALYs as opposed to DALYs for ONBOIDS, we computed DALYs (incorporating age-weighting, discounting at a rate of 3%, standard GBD life expectancy, and disability weights from previous studies) for the top 20 most burdensome infectious agents. The results were consistent with our main analysis and are provided in Appendix B.

Uncertainty in the HALY estimates

HALY calculations require numerous estimates from a wide range of data sources; therefore, it is not possible to accurately quantify the uncertainty for these estimates in the traditional manner (e.g., 95% confidence intervals). While a certain degree of uncertainty is inherent in all HALY estimates, it is accepted that only point estimates be provided, without attempting to incorporate all the uncertainty associated with the estimates.

2.2 APPROACHES TO ASSESSING DISEASE BURDEN

Incidence-based approach

In the incidence-based approach to disease burden calculations, all new cases are counted in an average year and all health outcomes (including those in future years) are assigned to the initial event. One major assumption of this approach is that the incidence, mortality and progression of diseases will be unchanged over time. The incidence-based approach contrasts with the prevalence-based approach in which the health status of a population at a specific point of time is assessed, possibly followed by attribution of the prevalent diseases to etiological agents or conditions. In the steady state situation there should be no difference between the approaches. For the majority of pathogens in this study, the incidence-based approach was used to calculate disease burden. However, we used a prevalence-based approach to calculate the burden of HPV because the transition parameters from HPV infection to the various HPV-related cancers have not yet been delineated.

Pathogen-based approach

Following the lead of the GBD study, most burden of disease studies measure the impact of certain agents (e.g., HIV, TB) and certain syndromes that are caused by multiple etiologic agents (e.g., pneumonia, septicaemia, acute otitis media). In this report, a syndrome is defined as a combination of symptoms and signs which may be caused by several different pathogens. For ONBOIDS, a deliberate decision was made to take a primarily pathogen-based approach (e.g., to quantify the burden of *Streptococcus pneumoniae* by attributing a certain proportion of cases of and deaths from pneumonia, septicaemia, acute otitis media and other conditions to *S. pneumoniae*). This approach facilitates the estimation of the potential impact of additional pathogen-specific interventions such as vaccines (e.g., vaccines against *S. pneumoniae*). However, to also allow comparability with other burden of disease studies and to assess the impact of non-pathogen-specific interventions, such as smoking cessation for pneumonia prevention, estimates of the burden of selected syndromes were also calculated (Appendix C).

2.3 AGE GROUPS

The following age groups were used for the YLL, YERF, and HALY calculations: less than 1 year, 1–4 years, and five-year age groups to 90 years or older. Due to limitations in data availability it was not always possible to obtain data for all age groups, in which case age groups were aggregated together.

2.4 TIME FRAME

Burden of disease studies generally identify a single year of study for which data are collected and estimates generated. Infectious diseases frequently exhibit substantial year-to-year variability due to episodic outbreaks, the introduction of interventions such as vaccines and other secular trends. Therefore, ONBOIDS used a three-year average for estimating annual disease incidence and mortality. Unfortunately, due to restrictions in data availability it was not possible to use the same three years for all of the data sources. Consequently, we used the three most current years of available data, as follows:

Mortality:	2003-2005
Reportable disease:	2005-2007
Health care utilization:	2005-2007
Cancer registry:	2005-2007

2.5 DATA SOURCES

The calculation of HALYs required information on mortality, disease incidence, health state distribution and health state duration, as well as severity weights associated with each health state. These estimates were collected from the following data sources:

Census estimates

The Census of Canada is administered in five-year intervals by Statistics Canada, which collects demographic and socioeconomic data on the population.[18] Census data for Ontario were used to create estimates of life expectancy for the population by the age groups specified in section 2.3.

Vital statistics

The Ontario Office of the Registrar General collects mortality data from death certificates completed by physicians. Due to legal reporting requirements, registration of deaths is considered to be virtually complete with regard to fact of death, but the accuracy of the cause of death is variable. Only a

single cause of death (also called the underlying cause), coded using the Tenth Revision of the International Classification of Diseases (ICD-10), was available for this study, and these mortality data were not linkable to other health administrative data. Availability of multiple causes of death allows more sophisticated analysis to be carried out. However, uncertainty in classifying cause of death may persist even with multiple causes of death, especially with infectious diseases. For example, people with chronic diseases such as heart disease and cancer may die from pneumonia, but their cause of death is often coded and attributed to one of their predisposing chronic conditions. Mortality records for Ontario residents who died outside of the province are not available. We also excluded deaths of non-residents that occurred in Ontario. The codes used for extracting the mortality data are listed in Appendix D.

Reportable disease data

Under the authority of the *Health Protection and Promotion Act* (HPPA), physicians and laboratories in Ontario are mandated to report all confirmed and suspect cases of a reportable disease to the Medical Officer of Health.[19] Since many infectious diseases of interest are reportable, estimates of disease incidence for a number of the diseases included in ONBOIDS were based on reportable disease data. On the other hand, not all infectious diseases included in the report are reportable, underreporting is known to occur for some reportable diseases, and sometimes only a subset of infections due to a pathogen are reportable (e.g., invasive *S. pneumoniae* rather than all *S. pneumoniae* cases).

In Ontario, all reportable disease data are stored in the integrated Public Health Information System (iPHIS), a centralized provincial reporting system. In 2005, iPHIS replaced the Reportable Disease Information System (RDIS), linking all Ontario public health units into a common database. Data for estimating disease incidence were obtained from the Public Health Protection and Prevention Branch, Public Health Division, Ontario Ministry of Health and Long-Term Care.

Health care utilization data

Because not all infectious diseases are reportable under the HPPA and as reportable disease data are known to underestimate burden of disease, health care utilization data (e.g., hospitalization and emergency department visit records, physician billing claims) were used to estimate the incidence of a subset of infectious diseases where reportable disease data were thought to be incomplete. In Ontario, all hospitalizations and medically necessary physician services are freely available under public health care insurance to almost the entire resident population. New immigrants and migrants, as well as Canadians who have been out of the country for seven months or more, are not covered by Ontario's health insurance plan until after three months of moving or returning to Ontario, so their burden may be missed.

For ONBOIDS, health care utilization data were collected from several large, validated databases.[20] Data were extracted from the Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD) and Same-Day Surgery database (CIHI-SDS), which contain detailed information on diagnoses and procedures for all acute care hospitalizations and same-day surgeries, respectively.[21, 22] Data on visits to emergency departments were obtained from CIHI's National Ambulatory Care Reporting System (NACRS).[23] Diagnoses in these datasets are coded using ICD-10. Data on physician visits were collected from the Ontario Health Insurance Plan (OHIP) physician billing claims database, which contains claims for outpatient clinic visits from approximately 98% of Ontario physicians.[24, 25] The diagnostic codes used in OHIP are generally similar to ICD-9 codes. A unique identifier (encrypted health card number) allows for de-identified linkage of individuals across datasets. A list of all ICD-10 and OHIP codes used in this study are listed in Appendix D.

Ontario Cancer Registry

The Ontario Cancer Registry (OCR) of Cancer Care Ontario registers all new cases of cancer in the province except for non-melanoma skin cancer.[26] The OCR identifies cancer cases from four major data sources: 1) hospital discharge or day surgery summaries with cancer diagnoses; 2) pathology reports with any mention of cancer; 3) records from the Regional Cancer Centres or Princess Margaret Hospital; and 4) death certificates with cancer as the underlying cause of death. The OCR was used to collect data on the incidence of cancerous health states for selected infectious diseases (i.e., cancers of the cervix, vulva, vagina, penis, anal canal and oropharynx for human papillomavirus (HPV); and hepatocellular carcinoma for hepatitis B and C).

Evaluating evidence from epidemiologic studies and the use of expert opinion

If infectious disease incidence or health state data were not available from any of the data sources listed above, then the medical databases MEDLINE and PubMed were searched for population-based epidemiologic studies regarding infectious disease incidence. The durations of the health states associated with an infectious disease were also estimated from epidemiologic studies. Ontario-specific studies were preferred, but studies from elsewhere in Canada or from other high-income countries were used, if necessary. The external validity of the studies was considered. Medical and infectious disease reference textbooks (e.g., *Harrison's Internal Medicine*,[27] *Heymann's Control of Communicable Diseases*[28]) were used to obtain estimates of the health state durations when the information was not found in any of the previously mentioned data sources. The expert groups were asked to validate all of the estimates for the parameters in their areas.

2.6 DISEASE LIST AND INCLUSION/ EXCLUSION CRITERIA

The list of infectious diseases studied was mostly adapted from the latest GBD study.[1] Diseases/ infectious agents were included if they were associated with severe morbidity or mortality (e.g., HIV) or if they were common in the Ontario population (e.g., *E. coli*). Diseases that were legally reportable to public health authorities (e.g., measles) were also considered for inclusion, as were diseases with a recent media or public profile in Ontario (e.g., West Nile virus). The included diseases and associated health states are listed in Exhibit 2.1, and the data sources used for each disease are listed in Exhibit 2.2. Diseases were divided into groups based on microbiologic taxonomy (e.g., mycoses), disease manifestation (e.g., hepatitis), mode of transmission (e.g., sexually transmitted infections) and intervention (e.g., vaccine-preventable diseases). The disease groups are not mutually exclusive, as some infectious agents could have been considered under more than one disease group (e.g., *S. pneumoniae* was included in the *common bacterial infections* group but could have been included in the *vaccine-preventable diseases* group).

The list is not exhaustive, with many infectious agents excluded from this report either because of data limitations or to maintain project timelines. Some of the more notable examples of excluded agents were *Helicobacter pylori*, non-tuberculosis mycobacteria, norovirus, rotavirus, Epstein-Barr virus and *Borrelia burgdorferi* (Lyme disease). However, these and other excluded pathogens certainly merit further study and could be incorporated into future versions of ONBOIDS.

Exhibit 2.1
List of infectious diseases and associated health states included in the Ontario Burden of Infectious Disease Study (ONBOIDS)

DISEASE GROUP/PATHOGEN	HEALTH STATES
Common bacterial infections	
Streptococcus pneumoniae	Bacterial meningitis + sequelae*; septic arthritis; otitis media; septicaemia; pneumonia; acute bronchitis; conjunctivitis
Escherichia coli	Acute prostatitis (males); cystitis; pyelonephritis; septicaemia; pneumonia; bacterial meningitis + sequelae*
Staphylococcus aureus	Endocarditis; septicaemia; pneumonia; septic arthritis; osteomyelitis; cellulitis
Group B streptococcus	Bacterial meningitis + sequelae*; septicaemia; sepsis of the newborn; septic arthritis; cellulitis; osteomyelitis
Group A streptococcus	Bacterial meningitis + sequelae*; septic arthritis; pharyngitis; cellulitis; necrotizing fasciitis; septicaemia; pneumonia
Haemophilus influenzae	Bacterial meningitis + sequelae*; septic arthritis; septicaemia; pneumonia; otitis media
Legionella	Pneumonia
Neisseria meningitidis	Bacterial meningitis + sequelae*
Other gram-negative bacteria	Acute prostatitis (males); cystitis; pyelonephritis; septicaemia; pneumonia; endocarditis; bacterial meningitis
Other gram-positive bacteria	Septicaemia; endocarditis; cystitis; pyelonephritis; acute prostatitis (males); septic arthritis
Viral hepatitis	
Hepatitis C virus	Chronic hepatitis; decompensated cirrhosis; hepatocellular cancer; transplant
Hepatitis B virus	Acute symptomatic episode; chronic hepatitis; decompensated cirrhosis; hepatocellular cancer; transplant
Hepatitis A virus	Uncomplicated episode; prolonged or relapsing episode; transplant
Sexually transmitted infections	
Human papillomavirus	Symptomatic anogenital warts; cancer of the cervix, vagina, vulva, penis, anal canal and oropharynx (including effects and after-effects of treatment)
HIV/AIDS	Diagnosed HIV (without AIDS); AIDS with mild complications; AIDS with moderate complications; AIDS with severe complications
Gonorrhea (*Neisseria gonorrhea*)	Ophthalmia neonatorum; urethritis (males); epididymitis/orchitis (males); cervicitis (females); pelvic inflammatory disease (females) + sequelae**
Chlamydia (*Chlamydia trachomatis*)	Ophthalmia neonatorum; neonatal penumonia; urethritis (males); epididymitis/orchitis (males); cervicitis (females); pelvic inflammatory disease (females) + sequelae**
Herpes simplex virus	Primary genital herpes syndrome; first symptomatic episode without primary genital herpes syndrome; recurrent genital herpes; neonatal herpes; encephalitis
Syphilis (*Treponema pallidum*)	Primary syphilis; secondary syphilis; neurosyphilis; congenital syphilis

Exhibit 2.1 (CONTINUED)
List of infectious diseases and associated health states included in the Ontario Burden of Infectious Disease Study (ONBOIDS)

DISEASE GROUP/PATHOGEN	HEALTH STATES
Viral respiratory infections	
Influenza	Otitis media; upper respiratory tract infection; pneumonia; acute bronchitis; bronchiolitis
Rhinoviruses	Upper respiratory tract infection; otitis media; bronchiolitis (children); acute bronchitis
Respiratory syncytial virus	Upper respiratory tract infection; otitis media; bronchiolitis (children); acute bronchitis; pneumonia
Parainfluenza virus	Upper respiratory tract infection; otitis media; acute bronchitis; pneumonia
Adenovirus	Upper respiratory tract infection; otitis media; bronchiolitis; pneumonia; conjunctivitis
Coronaviruses	Upper respiratory tract infection; acute bronchitis
Intestinal infections	
Clostridium difficile	Enterocolitis; post-colectomy
Campylobacter	Gastroenteritis, mild; gastroenteritis, moderate; gastroenteritis, severe; reactive arthritis; Guillain Barré syndrome; inflammatory bowel disease
Salmonella	Gastroenteritis, mild; gastroenteritis, moderate; gastroenteritis, severe; septicaemia
Listeria	Gastroenteritis; septicaemia; bacterial meningitis
Giardia lamblia	Infectious episode with acute diarrhea; chronic giardiasis (diarrhea)
Shigella	Gastroenteritis
E. coli O157:H7	Non-bloody diarrhea; bloody diarrhea; haemolytic uraemic syndrome; end-stage renal disease
Yersinia enterocolitica	Gastroenteritis; mesenteric adenitis
Cryptosporidium	Gastroenteritis
Cyclospora cayetensis	Gastroenteritis
Vaccine-preventable diseases	
Varicella zoster virus	Acute varicella episode; varicella with complications; acute zoster episode; zoster with complications
Pertussis (*Bordetella pertussis*)	Acute episode; pneumonia; seizure disorder
Poliovirus	Acute episode; long-term sequelae (paralysis)
Rubella	Infectious episode; congenital rubella syndrome
Mumps	Acute episode; orchitis (males); meningitis; deafness; encephalitis
Tetanus (*Clostridium tetani*)	Acute episode

Exhibit 2.1 (CONTINUED)
List of infectious diseases and associated health states included in the Ontario Burden of Infectious Disease Study (ONBOIDS)

DISEASE GROUP/PATHOGEN	HEALTH STATES
Measles	Acute episode; otitis media; encephalitis; pneumonia
Diphtheria (*Corynebacterium diphtheriae*)	Infectious episode; neurological complications
Tuberculosis	
Mycobacterium tuberculosis	Pre-diagnosed pulmonary infection; pulmonary infection (treated, in isolation); pulmonary infection (treated, not in isolation); extra-pulmonary infection (lymph node); extra-pulmonary infection (non-lymph node)
Mycoses	
Candida	Candidiasis, non-invasive; candidiasis, semi-invasive; candidiasis, invasive
Pneumocystis jiroveci (formerly PCP)	Pneumocystosis
Aspergillus	Aspergillosis, non-invasive and unspecified; aspergillosis, pulmonary invasive; aspergillosis, non-pulmonary invasive
Blastomyces	Blastomycosis, pulmonary and unspecified; blastomycosis, disseminated
Histoplasma	Histoplasmosis
Vector-borne and imported infections	
West Nile virus	West Nile fever; West Nile neuroinvasive disease; long-term neurological complications
Dengue	Dengue fever
Malaria	*Plasmodium falciparum*, not severe; *P.falciparum,* severe; Non-*P.falciparum* malaria
Typhoid/Paratyphoid fever (*Salmonella typhi/paratyphi*)	Infectious episode

* Seizure disorder, motor deficits, deafness
** Ectopic pregnancy, infertility

Exhibit 2.2

Data sources used to estimate disease incidence for each infectious agent in the Ontario Burden of Infectious Disease Study (ONBOIDS)

DISEASE/INFECTIOUS AGENT	iPHIS	Adjusted*	Health Care Utilization Data	Ontario Cancer Registry	Epidemiologic Studies	Statistical/ Simulation Models
Common bacterial infections						
Streptococcus pneumoniae			x			
Escherichia coli			x			
Staphylococcus aureus			x			
Group B streptococcus			x			
Group A streptococcus			x			
Haemophilus influenzae			x			
Legionella			x			
Neisseria meningitidis			x			
Other gram-negative bacteria			x			
Other gram-positive bacteria			x			
Viral hepatitis						
Hepatitis C virus				x		x
Hepatitis B virus				x		x
Hepatitis A virus	x					
Sexually transmitted infections						
Human papillomavirus				x	x	
HIV/AIDS						x
Gonorrhea (*Neisseria gonorrhea*)	x		x			
Chlamydia (*Chlamydia trachomatis*)	x		x			
Herpes simplex virus	x				x	
Syphilis (*Treponema pallidum*)	x					
Viral respiratory infections						
Influenza			x			
Rhinoviruses			x			
Respiratory syncytial virus			x			
Parainfluenza virus			x			
Adenovirus			x			
Coronaviruses			x			

Exhibit 2.2 (CONTINUED)
Data sources used to estimate disease incidence for each infectious agent in the Ontario Burden of Infectious Disease Study (ONBOIDS)

DISEASE/INFECTIOUS AGENT	iPHIS	Adjusted*	Health Care Utilization Data	Ontario Cancer Registry	Epidemiologic Studies	Statistical/ Simulation Models
Intestinal infections						
Clostridium difficile			x			
Campylobacter	x	x				
Salmonella	x	x				
Listeria	x					
Giardia lamblia	x					
Shigella	x	x				
E. coli O 157:H7	x	x				
Yesinia enterocolitica	x					
Cryptosporidium	x					
Cyclospora cayetensis	x					
Vaccine-preventable diseases						
Varicella zoster virus		x	x			
Pertussis (*Bordetella pertussis*)	x	x				
Poliovirus	x					
Rubella	x					
Mumps	x					
Tetanus (*Clostridium tetani*)	x					
Measles	x					
Diphtheria (*Corynebacterium diphtheriae*)	x					
Tuberculosis						
Mycobacterium tuberculosis	x					
Mycoses						
Candida			x			
Pneumocystis jiroveci (formerly PCP)			x			
Aspergillus			x			
Blastomyces			x			
Histoplasma			x			

Exhibit 2.2 (CONTINUED)
Data sources used to estimate disease incidence for each infectious agent in the Ontario Burden of Infectious Disease Study (ONBOIDS)

DISEASE/INFECTIOUS AGENT	iPHIS	Adjusted*	Health Care Utilization Data	Ontario Cancer Registry	Epidemiologic Studies	Statistical/ Simulation Models
Vector-borne and imported infections						
West Nile Virus	x					
Dengue			x			
Malaria	x					
Typhoid/Paratyphoid fever (*Salmonella typhi/paratyphi*)	x					
Syndromes due to other agents						
Pneumonia due to other agents			x			
Endocarditis due to other agents			x			
Septicaemia due to other agents			x			
Encephalitis due to other agents			x			
Acute bronchitis due to other agents			x			
Upper respiratory infections due to other agents			x			
Necrotizing fasciitis due to other agents			x			
Urinary tract infections due to other agents			x			
Cellulitis due to other agents			x			
Pharyngitis due to other agents			x			
Osteomyelitis due to other agents			x			
Otitis media due to other agents			x			
Conjunctivitis due to other agents			x			
Bacterial meningitis due to other agents			x			
Septic arthritis due to other agents			x			
Bronchiolitis due to other agents			x			

iPHIS = Integrated Public Health Information System
* adjusted for underreporting/underdiagnosis

2.7 ESTIMATION OF INCIDENCE AND MORTALITY

Details for estimating the incidence of and mortality for each disease are outlined in Chapter 4. In general, disease-specific mortality estimates were extracted from vital statistics data for all infectious agents. Estimates of non-fatal disease incidence came from multiple data sources (Exhibit 2.2). The majority of infectious disease incidence estimates came from reported disease counts and from episode counts observed in health care utilization datasets. Infections are generally of short duration, therefore these counts can be considered incident cases. For a few of the infectious agents, we adjusted reported disease counts for underreporting. Lastly, for a few diseases (HIV, hepatitis B and C) the methodology and expertise existed to use statistical or simulation models to generate more accurate estimates of disease incidence and their sequelae.

The etiologic agent-based approach

The etiologic agent-based approach (abridged as the "agent-based approach") begins with case counts of a confirmed etiologic agent. This often required reportable disease counts from iPHIS, which were averaged over three years (2005–2007) to generate an annual estimate of incidence. Where possible, we adjusted for underreporting using estimates from epidemiologic studies. We also used epidemiologic studies and expert opinion to determine the proportions of cases that would progress through various health states.

The syndrome-based approach

Many of the included conditions refer to syndromes where etiologic agents are frequently not identified (e.g., pneumonia). In these cases, epidemiologic studies and expert opinion were used to determine the proportions of the syndrome attributable to various etiologic agents. Since this method starts with counts of non-specific syndromes, we refer to this method of estimating disease incidence as the "syndrome-based approach."

When reportable disease data were unavailable and/or were identified as being insufficiently comprehensive (e.g., diseases where only invasive infections were deemed reportable), health care utilization data were used to estimate disease incidence. The three most recent years of hospitalization, same-day surgery, emergency department, and physician billing claims data were searched for the presence of diagnostic codes corresponding to the infectious diseases of interest. We looked for the relevant codes in all diagnostic codes, not just the one deemed to be the most responsible diagnosis. For each disease where administrative data were used, an episode length was established. An episode length was defined as the amount of time that must have elapsed between occurrences of the infection in the health care utilization data to be considered separate events in a single individual. Infections that occurred before the episode length had elapsed were considered part of the same episode. As per reportable diseases, event counts were averaged over the three years of data collected to generate an annual estimate of incidence.

The modeling approach

It is a considerable challenge to accurately estimate the number of new infections from HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) that occur annually in Ontario. Aside from the standard issues associated with underreporting of diseases, reported cases of HIV, HBV and HCV do not necessarily represent new infections. In fact, the majority of new diagnoses are among people who were infected in the past, and sometimes in the distant past. Thus, the numbers of cases reported to public health authorities, even if they were complete, are not an accurate reflection of the number of new infections. Furthermore, this approach does not capture the burden of prevalent chronic infections.

To overcome these limitations of the data, actuarial modeling studies were used to estimate the numbers of incident infections and the sequelae related to these infectious agents. These models incorporated data from multiple sources for population demographics, disease prevalence and incidence (adjusted for underreporting), and transition parameters. Further details about these models are presented in the sections specific to infectious agents in Chapter 4.

Overall Results and Interpretation

We estimated that infectious diseases accounted for 82,881 health-adjusted life years (HALYs) annually, with 68,213 years of life lost due to premature mortality (YLL) and 14,668 year-equivalents of reduced functioning (YERF).

Common bacterial infections accounted for the greatest proportion of the total HALYs among the 10 disease groups presented in Exhibit 3.1. The top three disease groups (common bacterial infections, viral hepatitis, sexually transmitted infections) accounted for 73% of the total HALYs. For all disease groups—except vaccine-preventable diseases (VPDs)—YLL accounted for a greater burden than YERF.

Females accounted for more HALYs than males for 60% of the disease groups. The exceptions were viral hepatitis, tuberculosis, mycoses and vector-borne and imported infections—where men accounted for more HALYs than women (Exhibit 3.2). Sex-specific differences in disease burden are discussed further in section 3.4.

Exhibit 3.1
Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs), by disease group

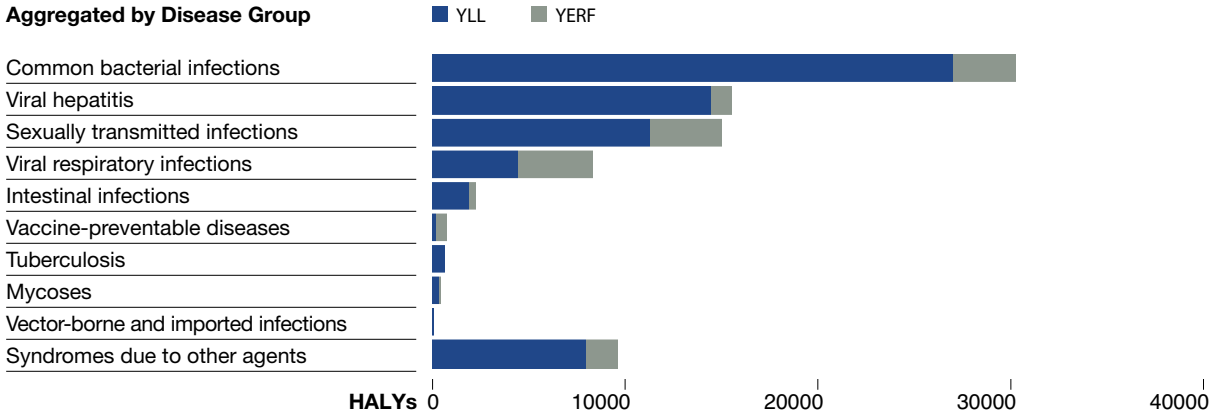
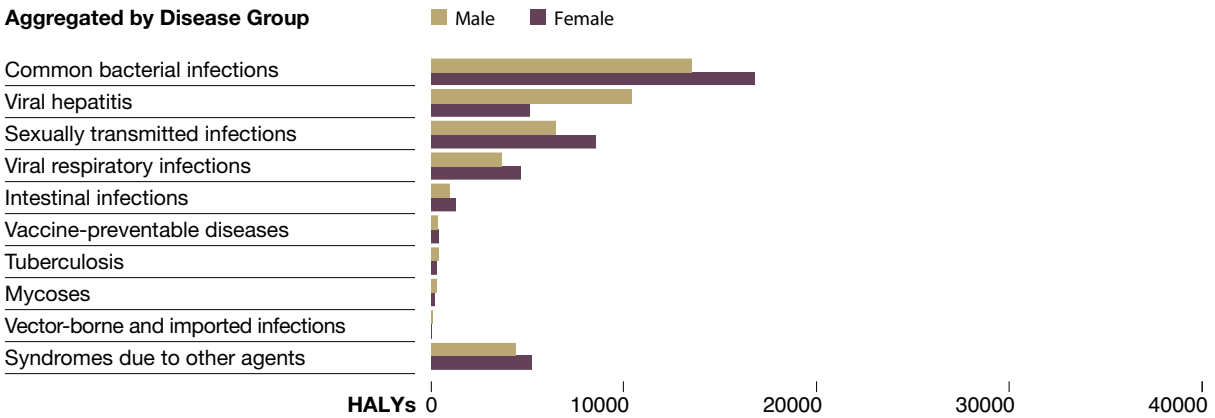


Exhibit 3.2
Health-adjusted life years (HALYs), by disease group and sex



Among the selected infectious disease syndromes, pneumonia accounted for the greatest proportion of total HALYs (Exhibit 3.3). YLL accounted for a greater burden than YERF for most syndromes. The exceptions were acute bronchitis, upper respiratory tract infections, otitis media, pharyngitis and conjunctivitis—very common conditions that rarely lead to death. The top three syndromes (pneumonia, septicaemia, urinary tract infections) accounted for 73% of the total syndrome HALYs. The burden of disease for most syndromes was only slightly higher for females; for urinary tract infections, the burden for females was more than twice as high (Exhibit 3.4).

Exhibit 3.3

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs), by infectious disease syndrome

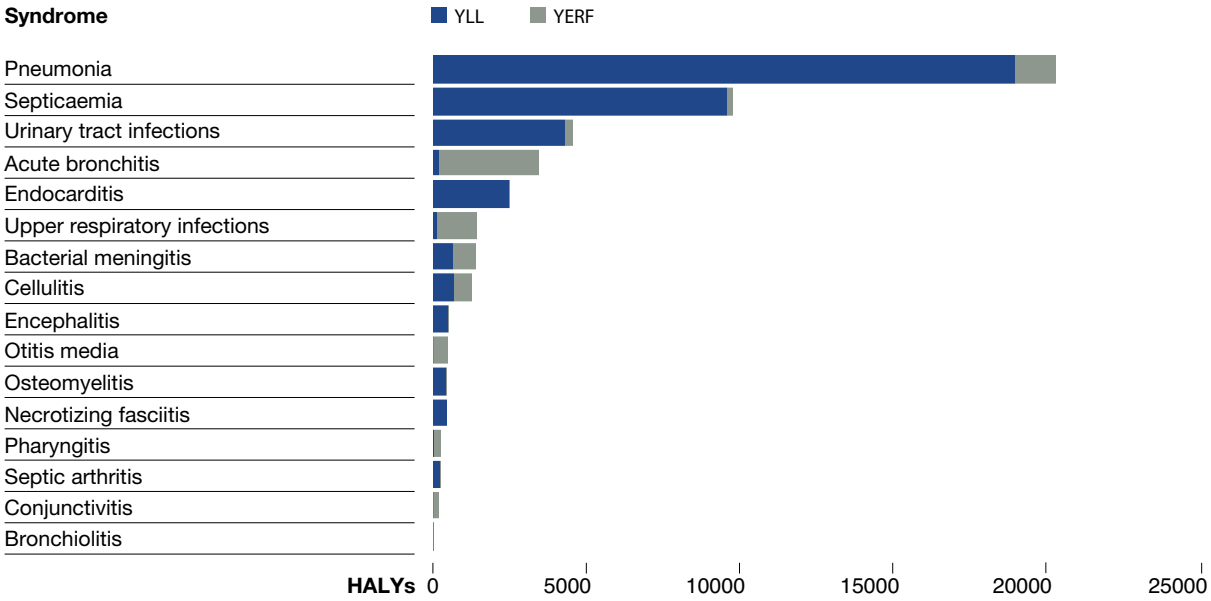
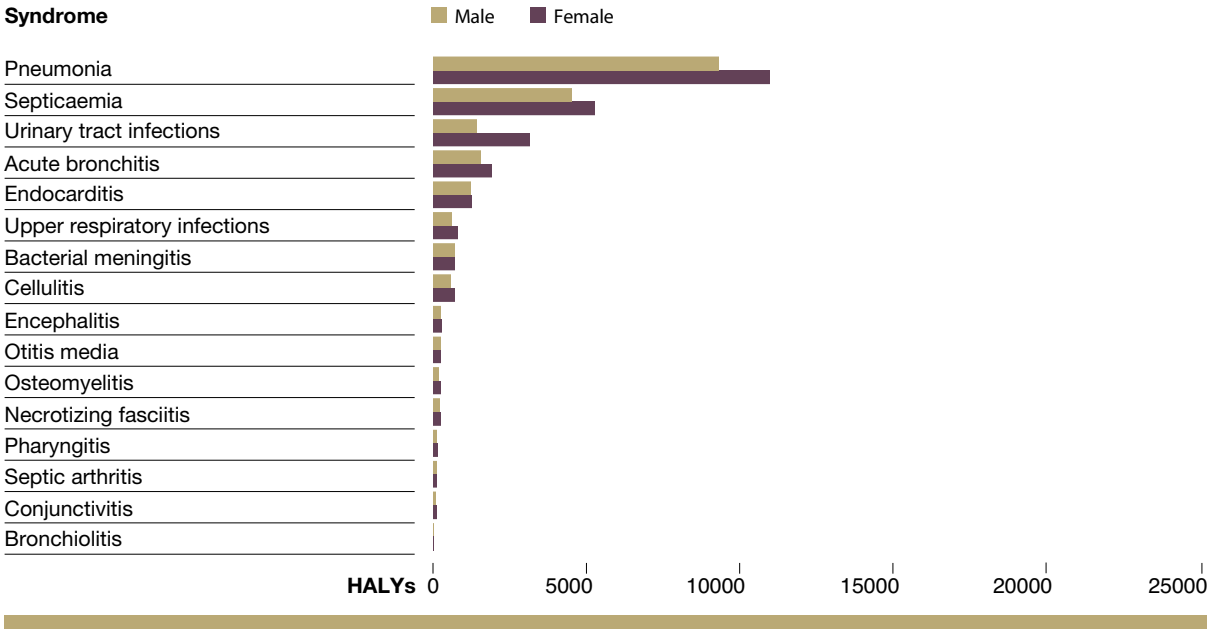


Exhibit 3.4

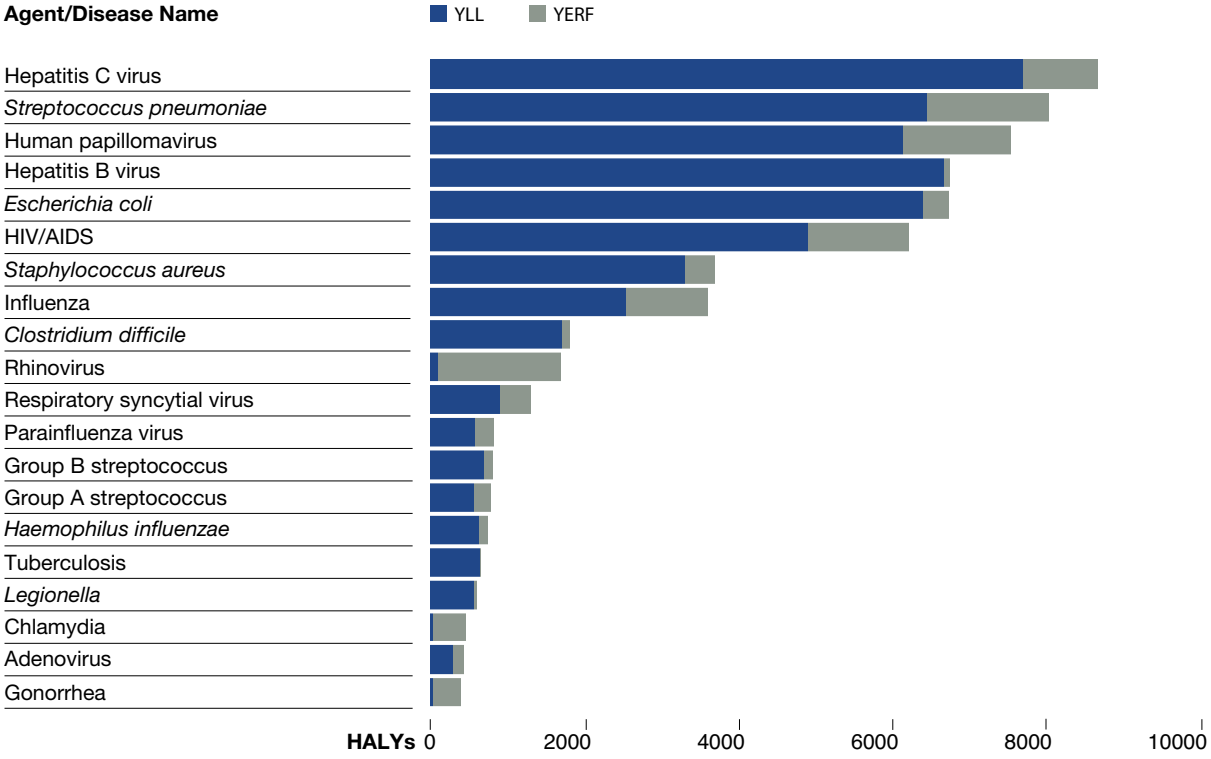
Health-adjusted life years (HALYs), by infectious disease syndrome and sex



The top 20 pathogens ranked by disease burden are shown in Exhibit 3.5. Hepatitis C virus was the highest-ranked pathogen in terms of disease burden, followed by *Streptococcus pneumoniae* (*S. pneumoniae*) and human papillomavirus (HPV). For most of the pathogens ranked in the top 20, YLL contributed more to disease burden than YERF, with the exception of rhinovirus, chlamydia and gonorrhea.

Exhibit 3.5

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for the top 20 pathogens, ranked by disease burden



The top 10 pathogens accounted for approximately 67% of total HALYs, and the top 20 pathogens accounted for 75% (Exhibit 3.6). Nearly half of the burden of infectious disease in Ontario could be attributed to five pathogens: hepatitis C virus (HCV), HPV, *S. pneumoniae*, hepatitis B virus (HBV) and *Escherichia coli* (*E. Coli*). Only 14 specific pathogens contributed 1% or more to the total HALYs, while 21 pathogens contributed less than 0.1% to the total HALYs estimated.

Exhibit 3.6

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF), number and percentage of total annual health-adjusted life years (HALYs) for each pathogen, ranked by disease burden

Rank	Pathogen	YLL	YERF	HALYs	% of Total HALYs
1	Hepatitis C virus	7,729	983	8,713	10.5
2	*Streptococcus pneumoniae*	6,475	1,601	8,076	9.7
3	Human papillomavirus	6,167	1,418	7,585	9.2
4	Hepatitis B virus	6,698	86	6,785	8.2
5	*Escherichia coli*	6,430	341	6,771	8.2
6	HIV/AIDS*	4,929	1,312	6,242	7.5
7	*Staphylococcus aureus*	3,320	400	3,720	4.5
8	Influenza	2,548	1,076	3,624	4.4
9	*Clostridium difficile*	1,721	107	1,828	2.2
10	Rhinovirus	95	1,615	1,710	2.1
11	Respiratory syncytial virus	914	397	1,310	1.6
12	Parainfluenza virus	581	259	840	1.0
13	Group B streptococcus	700	123	823	1.0
14	Group A streptococcus	574	216	791	1.0
15	*Haemophilus influenzae*	628	125	753	0.9
16	Tuberculosis	647	15	662	0.8
17	*Legionella*	570	40	609	0.7
18	Chlamydia	28	442	470	0.6
19	Adenovirus	287	150	437	0.5
20	Gonorrhea	27	371	398	0.5
21	Varicella	89	303	392	0.5
22	Coronavirus	23	369	392	0.5
23	*Neisseria meningitidis*	211	152	363	0.4
24	Herpes virus	136	138	274	0.3
25	Pertussis	0	220	220	0.3
26	Candida	104	91	195	0.2
27	*Campylobacter*	2	144	146	0.2
28	Poliomyelitis	117	0	117	0.1
29	*Pneumocystis jiroveci*	111	2	113	0.1
30	*Salmonella*	66	42	108	0.1
31	*Aspergillus*	49	31	79	0.1
32	West Nile virus	55	15	70	0.1
33	*Blastomyces*	59	2	61	0.1
34	*Listeria*	57	1	57	0.1
35	*Giardia*	0	52	52	0.1
36	*Shigella*	24	4	28	0.0
37	Hepatitis A	0	22	22	0.0
38	Syphilis (*Treponema pallidum*)	0	18	18	0.0

*Human immunodeficiency virus/Acquired immunodeficiency syndrome

Exhibit 3.6 (CONTINUED)
Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF), number and percentage of total annual health-adjusted life years (HALYs) for each pathogen, ranked by disease burden

Rank	Pathogen	YLL	YERF	HALYs	% of Total HALYs
39	*E. coli* O157	0	17	17	0.0
40	Dengue	13	0	13	0.0
41	Malaria	6	0	6	0.0
42	*Histoplasma*	0	6	6	0.0
43	Rubella	0	2	2	0.0
44	*Yersinia*	0	1	1	0.0
45	Typhoid/Paratyphoid	0	1	1	0.0
46	*Cryptosporidium*	0	0	0	0.0
47	*Cyclospora cayetensis*	0	0	0	0.0
48	Tetanus	0	0	0	0.0
49	Mumps	0	0	0	0.0
50	Measles	0	0	0	0.0
51	Diphtheria	0	0	0	0.0
–	Pneumonia**	5,161	324	5,484	6.6
–	Other gram-negative bacteria	4,505	219	4,725	5.7
–	Other gram-positive bacteria	3,558	74	3,632	4.4
–	Endocarditis**	741	10	751	0.9
–	Septicaemia**	594	13	606	0.7
–	Encephalitis**	391	26	417	0.5
–	Upper respiratory infections**	25	327	353	0.4
–	Necrotizing fasciitis**	344	3	347	0.4
–	Acute bronchitis**	9	278	287	0.3
–	Urinary tract infections**	266	17	283	0.3
–	Cellulitis**	133	112	244	0.3
–	Pharyngitis**	6	220	226	0.3
–	Osteomyelitis**	196	21	217	0.3
–	Otitis media**	0	137	137	0.2
–	Conjunctivitis**	0	123	123	0.1
–	Bacterial meningitis**	29	47	76	0.1
–	Septic arthritis**	64	6	70	0.1
–	Bronchiolitis**	0	1	1	0.0
	Total	**68,213**	**14,668**	**82,881**	**100.0**

**due to other agents

The nine pathogens that caused the greatest number of deaths also caused the greatest disease burden, with some change in ranking order (Exhibit 3.7).

Exhibit 3.7

Number and percentage of average annual deaths for each pathogen

Rank	Pathogen	# of Deaths	% of Total Deaths
1	*Streptococcus pneumoniae*	632	12.9
2	*Escherichia coli*	600	12.3
3	Hepatitis C virus	369	7.5
4	Hepatitis B virus	346	7.1
5	Influenza	272	5.6
6	*Staphylococcus aureus*	268	5.5
7	Human papillomavirus	254	5.2
8	*Clostridium difficile*	167	3.4
9	HIV/AIDS*	133	2.7
10	Respiratory syncytial virus	96	2.0
11	*Haemophilus influenzae*	62	1.3
12	Parainfluenza virus	59	1.2
13	*Legionella*	59	1.2
14	Group A streptococcus	48	1.0
15	Tuberculosis	41	0.8
16	Adenovirus	29	0.6
17	Group B streptococcus	18	0.4
18	Poliomyelitis	8	0.2
19	*Neisseria meningitidis*	7	0.1
20	Herpes virus	7	0.1
21	*Candida*	7	0.1
22	Varicella	6	0.1
23	Rhinovirus	5	0.1
24	*Pneumocystis jiroveci*	4	0.1
25	West Nile virus	4	0.1
26	*Aspergillus*	3	0.1
27	*Salmonella*	2	0.0
28	*Blastomyces*	2	0.0
29	*Listeria*	2	0.0
30	Chlamydia	1	0.0
31	Gonorrhea	1	0.0
32	Coronavirus	1	0.0
33	Pertussis	0	0.0
34	*Campylobacter*	0	0.0
35	*Giardia*	0	0.0
36	*Shigella*	0	0.0
37	Hepatitis A	0	0.0
38	Syphilis (*Treponema pallidum*)	0	0.0
39	E. coli O157	0	0.0
40	Dengue	0	0.0
41	Malaria	0	0.0
42	*Histoplasma*	0	0.0
43	Rubella	0	0.0
44	Yersinia	0	0.0
45	Typhoid/Paratyphoid	0	0.0

*Human immunodeficiency virus/Acquired immunodeficiency syndrome

Exhibit 3.7 (CONTINUED)
Number and percentage of average annual deaths for each pathogen

Rank	Pathogen	# of Deaths	% of Total Deaths
46	*Cryptosporidium*	0	0.0
47	*Cyclospora cayetensis*	0	0.0
48	Tetanus	0	0.0
49	Mumps	0	0.0
50	Measles	0	0.0
51	Diphtheria	0	0.0
–	Pneumonia**	529	10.8
–	Other gram-negative bacteria	400	8.2
–	Other gram-positive bacteria	264	5.4
–	Endocarditis**	53	1.1
–	Septicaemia**	43	0.9
–	Urinary tract infections**	28	0.6
–	Osteomyelitis**	17	0.3
–	Necrotizing fasciitis**	15	0.3
–	Encephalitis**	14	0.3
–	Cellulitis**	12	0.2
–	Septic arthritis**	5	0.1
–	Upper respiratory infections**	1	0.0
–	Pharyngitis**	1	0.0
–	Bacterial meningitis**	1	0.0
–	Bronchitis**	0	0.0
–	Otitis media**	0	0.0
–	Conjunctivitis**	0	0.0
–	Bronchiolitis**	0	0.0
	Total	**4,896**	**100.0**

**due to other agents

The list of most common infections is dominated by respiratory viruses, with rhinovirus, influenza, coronavirus, respiratory syncytial virus, parainfluenza virus and adenovirus among the top 10 (Exhibit 3.8). Others in the top 10 include *S. pneumoniae*, *E. coli*, *Staphylococcus aureus* (*S. aureus*) and Group A streptococcus.

Exhibit 3.8

Number and percentage of average annual estimated incident cases for each pathogen

Rank	Pathogen	# of Incident Cases	% of Total Incident Cases
1	Rhinovirus	1,615,561	22.4
2	Influenza	621,151	8.6
3	*Streptococcus pneumoniae*	518,703	7.2
4	Coronavirus	461,767	6.4
5	*Escherichia coli*	451,268	6.3
6	Respiratory syncytial virus	341,471	4.7
7	Parainfluenza virus	253,292	3.5
8	Adenovirus	203,393	2.8
9	*Staphylococcus aureus*	158,443	2.2
10	Group A streptococcus	118,989	1.7
11	Varicella*	116,049	1.6
12	*Haemophilus influenzae*	105,076	1.5
13	*Campylobacter*	88,566	1.2
14	*Candida*	71,616	1.0
15	Chlamydia	61,761	0.9
16	*Salmonella*	34,693	0.5
17	Gonorrhea	32,234	0.4
18	Human papillomavirus	15,756	0.2
19	Herpes virus	14,677	0.2
20	Pertussis	8,874	0.1
21	*Legionella*	7,574	0.1
22	Group B streptococcus	6,764	0.1
23	*Clostridium difficile*	5,364	0.1
24	*Shigella*	5,120	0.1
25	Hepatitis C virus	3,469	0.0
26	*E. coli* O157	3,188	0.0
27	HIV/AIDS**	1,965	0.0
28	*Giardia*	1,596	0.0
29	Hepatitis A	795	0.0
30	Tuberculosis	673	0.0
31	Syphilis (*Treponema pallidum*)	367	0.0
32	*Cryptosporidium*	357	0.0
33	*Yersinia*	327	0.0
34	*Histoplasma*	245	0.0
35	*Aspergillus*	235	0.0
36	Hepatitis B virus	213	0.0
37	Malaria	183	0.0
38	*Pneumocystis jiroveci*	177	0.0
39	*Neisseria meningitidis*	159	0.0
40	Typhoid/Paratyphoid	133	0.0

* Includes recurrent clinical disease caused by prior infections (i.e., herpes zoster [shingles])

**Human immunodeficiency virus/Acquired immunodeficiency syndrome

Exhibit 3.8 (CONTINUED)
Number and percentage of average annual estimated incident cases for each pathogen

Rank	Pathogen	# of Incident Cases	% of Total Incident Cases
41	*Cyclospora cayetensis*	106	0.0
42	Rubella	105	0.0
43	*Blastomyces*	55	0.0
44	West Nile virus	50	0.0
45	*Listeria*	39	0.0
46	Mumps	26	0.0
47	Dengue	14	0.0
48	Measles	3	0.0
49	Tetanus	1	0.0
50	Poliomyelitis	0	0.0
51	Diphtheria	0	0.0
–	Upper respiratory infections***	799,472	11.1
–	Conjunctivitis***	277,484	3.9
–	Pharyngitis***	221,030	3.1
–	Otitis media***	213,114	3.0
–	Bronchitis***	83,914	1.2
–	Other gram-negative bacteria	83,532	1.2
–	Pneumonia***	61,852	0.9
–	Cellulitis***	55,494	0.8
–	Urinary tract infections***	33,979	0.5
–	Other gram-positive bacteria	25,358	0.4
–	Osteomyelitis***	4,392	0.1
–	Septic arthritis***	1,053	0.0
–	Septicaemia***	966	0.0
–	Encephalitis***	898	0.0
–	Bronchiolitis***	570	0.0
–	Endocarditis***	385	0.0
–	Necrotizing fasciitis***	191	0.0
–	Bacterial meningitis***	22	0.0
	Total	**7,196,349**	**100.0**

***due to other agents

3.1 DEATH AND REDUCED FUNCTIONING

In keeping with other international studies this investigation used HALYs—conceptually similar to DALYs—as a summary measure of the burden of individual diseases on population health. HALYs and DALYs incorporate not only premature mortality, but also morbidity. For example, the Victorian Burden of Diseases Study determined that YLD (years of life lived with a disability) (343,671 [53%]) exceeded YLL (309,471 [47%]) when looking at all diseases and conditions.[15] For some diseases, disability accounts for an even greater proportion of disease burden (e.g., more than two-thirds of DALYs associated with diabetes mellitus, and more than nine-tenths of DALYs associated with depression).

Therefore, one of the most striking aspects of our study of infectious diseases in Ontario was the dominant burden of premature mortality (YLL) over reduced functioning (YERF). In Ontario, 82% of HALYs attributable to infectious diseases were from premature mortality (68,213 YLL), whereas only a small percentage (18%) of HALYs were related to reduced functioning (14,668 YERF). In fact, YLL exceeded YERF for 17 of the top 20 pathogens. Exceptions among the pathogens studied in ONBOIDS included rhinovirus, coronavirus, gonorrhea, chlamydia, varicella zoster virus, *Campylobacter*, and *Giardia*—where YERF exceeded YLL.

The amount that a disease reduces functioning is a consequence of disease incidence, severity and duration. The dominant impact of mortality over reduced functioning for the infectious diseases does not relate to low disease incidence; these diseases are remarkably common in our population, with a total of more than 7,000,000 episodes of infection per year. Nor does the dominance of mortality over reduced functioning relate to low severity weights for ill patients; for example, the weight for septicaemia (0.652) represents greater severity than receiving palliative care for cancer (0.516).[5] Instead, the low YERF impact of infectious diseases relates mostly to limited disease duration. Whereas patients with chronic illnesses can survive for many years in a disabled state, most infectious diseases either result in death relatively quickly or resolve with minimal long-term sequelae for survivors. Even if a particular disease has a severity weight approximating that of death (1.0), if the disease duration is only one week, one incident case of that disease would contribute only 0.02 YERF. In contrast, one case of a mild systemic illness with a severity weight near perfect health (0.1) could contribute 2.0 YERF if it lasts for 20 years.

Previous studies from Australia have suggested only a slight dominance of premature mortality over morbidity for infections, but not to the extent observed in our study.[4, 15] As a sensitivity analysis, we repeated our analysis using the standard GBD methodology and found much more parity between the contributions of premature mortality and morbidity (Appendix B). Using the GBD methodology (i.e., DALYs), premature mortality contributed only 49% of the total burden of the top 20 pathogens, whereas using the ONBOIDS methodology (i.e., HALYs), premature mortality contributed 82% of the total disease burden for these pathogens (Appendix B, Table B.2). These differences arise from substantial reductions in YLL for the pathogens that mainly cause deaths in elderly individuals due to the use of age-weighting and discounting, as well as increased YLD due to generally heavier weights used in health state valuation (i.e., the disability weights from previous GBD studies tend to be greater magnitude than the severity weights derived for ONBOIDS).

Given this uncertainty, we hesitate to recommend whether decision makers should focus their attention on preventing mortality versus morbidity when prioritizing interventions for a particular pathogen, except for pathogens where the results are consistent regardless of the methodology employed.

3.2 PATHOGEN-BASED AND SYNDROME-BASED PLANNING

A study of infectious diseases involves an added layer of complexity compared to other disease groups, because infections can be divided according to the causative agent (**pathogen-based approach**) or by the type of illness in the host (**syndrome-based approach**). When a patient is seen with any infectious syndrome, empiric treatment is often initiated without identification of the specific etiologic agent, especially when the most likely pathogens associated with a syndrome are well known or where the rapid initiation of treatment is felt to be important. Most pathogens can cause multiple syndromes in varying frequency, and most syndromes may be caused by multiple pathogens in varying frequency. For

example, *S. pneumoniae* is the most common cause of pneumonia, but there are many other causes of pneumonia, such as *Haemophilus influenzae* and *Legionella pneumophila*. This is also true of many other syndromes caused by *S. pneumoniae*, such as meningitis, septicaemia and otitis media.

The ONBOIDS approach has been predominantly pathogen-based, and has demonstrated that the most burdensome infectious pathogens include HCV, *S. pneumoniae*, HPV, *E. coli*, HBV, human immunodeficiency virus (HIV), *S. aureus* and influenza. These data are an important means to quantify the potential benefits of new vaccine development (e.g., for *S. aureus*) or by extending coverage with available vaccines (e.g., for influenza and HPV). They can also help define the potential benefit of other pathogen-specific prevention and treatment strategies. They do not, however, reflect the historical change in burden due to current vaccines against infectious diseases.

In addition, our data outline the infectious disease syndromes with the highest burden, including pneumonia, septicaemia and urinary tract infections. These results can help guide "horizontal" prevention methods that are independent of the causative pathogen. For example, many methods of preventing pneumonia, such as smoking cessation, are not pathogen-specific. Syndrome-based data may actually be more accurate for conditions for which a causative pathogen is usually not identified for individual cases. The approach may also be helpful in guiding the development of syndromic treatment protocols, as well as primary and secondary prevention strategies.

3.3 THE ENEMY WITHIN AND THE ENEMY WITHOUT: ENDOGENOUS AND EXOGENOUS PATHOGENS

One of the most concerning aspects of infectious diseases is their capacity to transfer from one person to another. Communicability is exemplified by several of the top pathogens in Ontario, such as HPV (sexual), HIV and hepatitis viruses (sexual, blood-borne and mother-to-child transmission) and influenza (respiratory transmission). However, not all infectious diseases result from transmission from an external (exogenous) source. Instead, many infectious diseases are caused by bacteria that constitute part of the normal flora of the skin, mouth, genitalia or gastrointestinal tract (endogenous). For example, our intestine is home to about 100 trillion bacteria, more than the number of human cells in the body.[29] Normal residents of the intestine, *E. coli* and other gram-negative bacteria are responsible for nearly 11,000 potential years of life lost per year in Ontario. Preventing transmission of more virulent or drug-resistant strains between individuals may help to reduce a portion of disease burden from these bacteria, but greater gains may be achieved by strategies to prevent these bacteria from gaining access to normally sterile body sites. For example, minimizing the use of urinary and vascular catheters among hospitalized patients can help prevent some of the kidney and bloodstream infections caused by these bacteria. In general, ONBOIDS indicates that the concept of exogenous and endogenous pathogens is an important consideration in policies involving infectious diseases since the preventive strategies and treatment interventions differ between these two groups.

3.4 GENDER LENS ON INFECTIOUS DISEASES BURDEN

The overall burden of infectious diseases in Ontario was relatively similar for males (40,416 HALYs) and females (42,465 HALYs); however, there were marked differences in the sex-specific burden for a number of individual pathogens and syndromes. Some of these sex differences have obvious biological explanations, such as the differential burden of HPV (cervical cancer in women) and urinary tract pathogens (shorter urethra in women). In contrast, many of the illnesses with greater burden among males would appear to relate to psychosocial rather than biological factors. The three pathogens exhibiting a large male predominance (HIV, HBV and HCV) are commonly associated with high-risk behaviours including unprotected sexual intercourse (among men who have sex with men, as well as heterosexual sexual encounters) and injection drug use. Other explanations for sex-specific differences may include a greater tendency for health-seeking behaviour among women,[30] a longer average life expectancy for women (more potential years of life to lose) and differences in the age structure between males and females. In general, these results indicate that some interventions may need to be targeted to the different sexes.

3.5 PUBLIC PERCEPTIONS AND PUBLIC HEALTH

This report highlights that the actual burden of individual pathogens is not necessarily proportionate to the attention they receive in the popular media. For example, West Nile virus and *Listeria* have received extensive media attention in recent years, yet they contributed only 70 (0.08%) and 57 (0.07%) HALYs, respectively. This may suggest that public communications ought to better reflect population burden, with more discussion related to more common agents and syndromes. Alternatively, it suggests that public notices appropriately account for more than just the quantity of disease burden, but also the preventability of the burden (e.g., meat processing and *Listeria*), and the fear associated with newly emerging infections (typified by West Nile virus).

Further work is required to understand public risk perception on the value of life. It is unlikely that Ontarians regard one YLL in an 80-year-old with influenza as equivalent to one YLL in a 10-year-old with meningococcal meningitis.[13,31]

3.6 PREVENTION PAST AND FUTURE

Our data must be interpreted both as a measure of past interventions and a compass for future interventions. For example, the low burden of measles, mumps, rubella, polio, diphtheria and tetanus should be considered strong evidence of the importance and success of vaccination programs.

It would be wrong to conclude that the low burden of illness associated with these diseases means they are not highly significant from a public health and resource allocation perspective. Among the potentially vaccine-preventable viral infections, HPV, HBV, influenza and varicella zoster virus merit further efforts to increase vaccine uptake, given the burden of disease associated with these pathogens. Furthermore, new vaccines are under development for several of the top causes of morbidity and mortality in Ontario (e.g., group B streptococcus, group A streptococcus).

This report also highlights a number of other important general avenues for intervention. Behavioural interventions may help prevent significant HALYs if rates of blood-borne and sexually transmitted pathogens can be reduced. The large burden imposed by common nosocomial pathogens (gram-negative bacteria, *S. aureus*, *C. difficile*) suggests that increasing attention must be paid to preventing infections among hospitalized patients. The findings in this report will help public health authorities place these risks into context.

The current estimated burdens of a number of infectious agents characterized by longer disease courses (e.g., HIV, HPV, HBV and HCV) relate partially to historic trends and/or imported infections; therefore, a proportion of these burdens may not necessarily represent current targets for prevention of incident infections in Ontario.

3.7 COMPARING ONBOIDS TO OTHER BURDEN OF DISEASE STUDIES IN CANADA

The Population Health Impact of Disease in Canada (PHI) group used a similar approach to ONBOIDS to quantify the burden of cancer in Canada in 2001.[5,6] Although the scope of this study was national, comparisons to ONBOIDS can be made by applying the proportion of the Canadian population living in Ontario (approximately 40%) to the HALYs.

In total, we estimated that infectious diseases accounted for 82,881 HALYs annually. The PHI group estimated 905,000 HALYs attributable to cancers diagnosed in 2001 in Canada,[5] or roughly 362,000 HALYs for Ontario. Therefore, the burden of all infectious diseases is approximately one-quarter of the burden of all malignancies diagnosed, although it should be noted that the burden of HPV-related cancers and hepatocellular carcinoma were included in both studies. The burden of all infectious diseases in Ontario is roughly equal to the burden calculated for lung cancer alone. HCV, the infectious disease calculated to account for the greatest number of HALYs at 8,713, was about equal to the burden of ovarian cancer (in 10th place amongst the cancers).

Although infectious diseases were calculated to have only approximately one-quarter of the burden of cancer in Ontario, it is important to highlight that the data sources used to capture cancer incidence and mortality are probably more comprehensive

and accurate than those used for infectious diseases. As noted in our study limitations (section 5.2), we believe that there is substantial underreporting and underdiagnosis of some infectious diseases (e.g., intestinal infections and influenza) and that some infectious disease deaths are not classified as such. These limitations may exist when estimating cancer incidence and mortality, although probably not to the extent of infectious diseases. Therefore, the burden of infectious diseases may be closer to the burden of cancers than demonstrated by these results. Regardless of the potential underestimation of infectious disease burden, the finding that infectious diseases have approximately one-quarter of the burden of cancers shows that infectious diseases still contribute substantially to the overall morbidity and mortality of Ontarians. Strategies that reduce both cancers and infectious disease may therefore be particularly important for resource allocation (e.g., smoking cessation to prevent cancer and pneumonia).

3.8 COMPARING ONBOIDS TO OTHER BURDEN OF INFECTIOUS DISEASE STUDIES

The European Centre for Disease Prevention and Control (ECDC) recently conducted a pilot study to determine the burden of seven infectious diseases (influenza, measles, HIV-infection, tuberculosis, campylobacterosis, salmonellosis and enterohaemorrhagic E. coli) on the continent.[3] Use of a per capita measure of burden (DALYs/HALYs per year per 100,000 population) facilitates comparisons of the burden of infectious disease between the studies. Similar to ONBOIDS, the ECDC study did not incorporate discounting or age-weighting in their primary analysis.

In ONBOIDS, we estimated the disease burden for all the pathogens in the ECDC pilot study. The seven common infectious diseases were ranked in a similar order between the two studies, with the exception of influenza, which was ranked much lower in the ECDC study due to their use of reported (laboratory-confirmed) cases of influenza instead of the syndrome-based approach or modeled estimates of influenza illness. Laboratory-confirmed cases of influenza likely underestimate the true incidence in the community, as only a small fraction of patients suspected of having influenza have specimens collected and tested.[32] As we would expect, the magnitude of burden attributable to tuberculosis in Europe was also very different from the burden of tuberculosis in Ontario, because the ECDC study included a number of Eastern European countries with a high prevalence of tuberculosis.[33] However, the burden of TB in Ontario is similar to the burden in the Netherlands and Sweden. A negligible burden of measles was also detected in the majority of European countries.

Comparisons to other burden of disease studies can be difficult due to differences in: 1) the outcome measure (HALYs vs. DALYs); 2) social value choices (age-weighting, discounting and different methods to calculate disability/severity weights for health states); and 3) methods used to address underreporting or infectious disease incidence and mortality. To facilitate comparisons to studies from other regions, the current report also included an additional analysis using the GBD methodology to calculate DALYs with full age-weighting, discounting and GBD disability weights (Appendix B). Using the burden per capita estimates, we can compare the burden of individual infectious pathogens that were assessed in both the Australian burden of disease study[4] and our ONBOIDS investigation:

- The burdens of HIV/AIDS and chlamydia were similar between Ontario and Australia.
- The burdens of HBV and HCV were nearly 2.5 times greater in Ontario compared to Australia.
- The burden of tuberculosis was nearly twice as high in Australia than in Ontario.

Some of the observed differences may represent true differences in disease incidence between Australia and Ontario, but some may relate to the different data sources, health states and methodologies used in the two studies.

CHAPTER 4

Methods and Results by Infectious Agent

Chapters 2 and 3 described the overall methods and results of ONBOIDS. This chapter provides a more detailed description of the methods and results for the disease burden of each infectious agent. A description of selected individual infectious syndromes can be found in Appendix C.

The following information is provided for each infectious agent in the study:

1. A brief description of the pathogen and its sequelae.
2. An outline of the data sources and methods used to calculate disease burden.
3. A table of parameters that specify the values used in the disease burden calculation.
4. A description of how disease burden was distributed among the Ontario population.
5. A discussion of some of the most pertinent limitations for calculating the pathogen-specific disease burden. (Study limitations are described in greater detail in Chapter 5.)

4.1 COMMON BACTERIAL INFECTIONS

Infectious agents assigned to this disease group generally have the potential to infect different anatomic sites and most are not reportable diseases (except when they manifest as invasive disease).

Within this disease group, *S. pneumoniae* was calculated to have the highest disease burden, followed by *E. coli* and *S. aureus* (Exhibit 4.1). Gram-negative bacteria other than *E. coli* also contributed a considerable collective burden. Most of the disease burden from common bacterial infections was from premature mortality. There was generally a higher burden from these common bacterial infections in females compared to males (Exhibit 4.2).

Exhibit 4.1

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for common bacterial infections

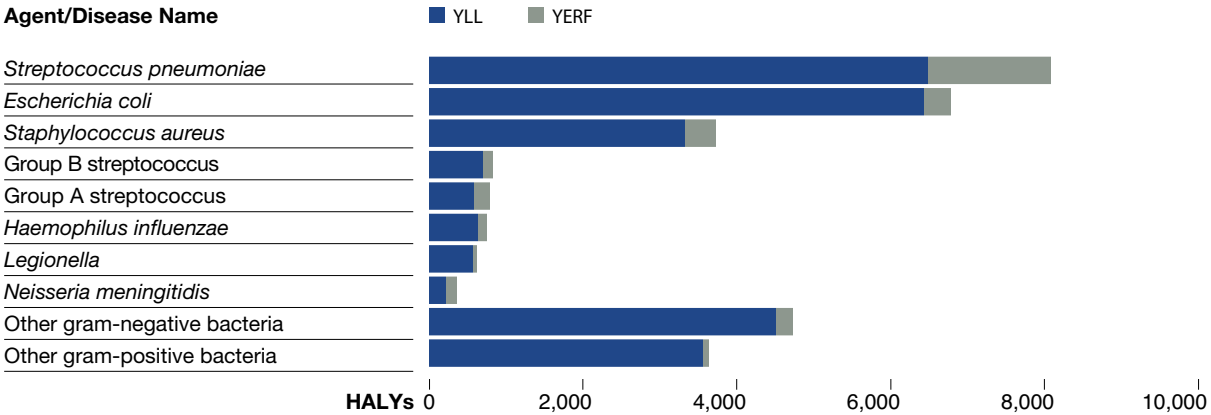
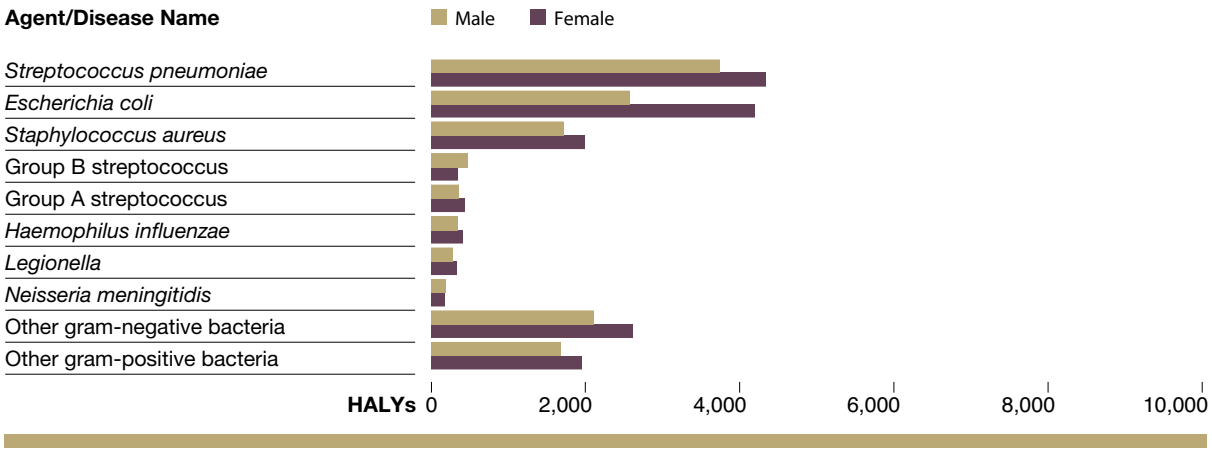


Exhibit 4.2

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for common bacterial infections, by sex



4.1.1. *STREPTOCOCCUS PNEUMONIAE*

S. pneumoniae (pneumococcus) is a gram-positive bacterium with a human reservoir, colonizing the nasopharynx of 5–10% of adults and 20–40% of children. It has multiple serotypes and causes a range of syndromes ranging in severity from mild to fatal. *S. pneumoniae* can cause upper respiratory tract infections, such as otitis media (middle ear infection), sinusitis (sinus infection), bronchitis (upper airway infection) and lower respiratory tract infections. This organism is the number one bacterial cause of pneumonia (lung infection) and meningitis (cerebrospinal fluid infection). It is also capable of producing invasive infection at many other sites. Variable levels of resistance have emerged among *S. pneumoniae* to most of the commonly used antibacterial drugs. A polysaccharide vaccine for 23 *S. pneumoniae* serotypes has been available for use in adults for many years. Between 2001 and the present, protein-conjugated vaccines for *S. pneumoniae* serotypes 7, 10 and 13 have been approved for use in children and high-risk groups.

Data sources and HALY calculation

As *S. pneumoniae* is often not confirmed with laboratory testing and is not a reportable disease unless it is invasive, we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes *S. pneumoniae* most commonly causes. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from *S. pneumoniae* infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to *S. pneumoniae* (to estimate both deaths and incident cases) and the duration of each health state.

Exhibit 4.3
Parameters for estimating disease burden due to *Streptococcus pneumoniae*

Health State	Percentage of Syndrome Attributable to *S. Pneumoniae*	Duration	Severity Weight	Episode Length*	Number of Episodes	Number of Deaths
Bacterial meningitis (BM)	32 (0–4 years) 45 (5–14 years) 51 (≥15 years)[34, 35]	2 weeks[27]	0.652	3 years	146	9
Sequelae of BM						
Seizures	24[35]	Permanent	0.039	N/A	35	0
Motor deficits	65[35]	Permanent	0.062	N/A	95	0
Deafness	9[36]	Permanent	0.071	N/A	13	0
Septicaemia	4.8[37]	1 week[38]	0.652	30 days	748	34
Pneumonia	30[39]	2 weeks[27]	0.136	30 days	75,742	586
Septic arthritis	1[40]	19 days[41]	0.108	60 days	35	0
Acute bronchitis	20[42]	2 weeks[43]	0.086	30 days	198,501	3
Otitis media	26[44]	4.5 days[45]	0.052	30 days	194,420	0
Conjunctivitis	12[46]	1 week[47]	0.023	15 days	48,968	0

* Episode length denotes the amount of time that must have elapsed between occurrences of the infection in the health care utilization data to be considered separate events in a single individual.

Estimated burden

We estimated annual averages of 632 deaths and 518,703 health care utilization episodes attributable to *S. pneumoniae*. The burden was slightly higher in females compared to males. Most of the burden was in individuals aged 65 or older. In particular, there were many pneumonia deaths among the elderly, and a high percentage of those deaths (30%) were caused by this pathogen.

Limitations

These estimates for the burden of *S. pneumoniae* are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. The assumption that the attributable fraction of the included syndromes for *S. pneumoniae* is the same for non-fatal cases as for fatal cases would likely lead to an underestimate of *S. pneumoniae* burden, since this pathogen is generally more virulent than other leading causes of meningitis and lower respiratory tract infection.

4.1.2. *ESCHERICHIA COLI (E. COLI)*

E. coli is a gram-negative bacillus and one of the most common constituents of the normal gastrointestinal tract. Some invasive strains of *E. coli* are not normal gastrointestinal flora and so can produce intestinal infection (e.g., enterohaemorrhagic *E. coli* O157:H7). However, even normal endogenous strains of *E. coli* can produce infection when they access areas outside of the bowel lumen. The most common infection produced by *E. coli* is cystitis (lower urinary tract infection [UTI]) or pyelonephritis (upper UTI), which can also be associated with septicaemia (bloodstream infection). Among hospitalized patients, skin and oropharnygeal colonization with gram-negative bacteria such as *E. coli* is very common, and in this context *E. coli* can contribute to a range of other syndromes that would not be common among non-hospitalized patients, such as *E. coli* pneumonia (lung infection). It is also a common cause of neonatal meningitis.

E. coli O157:H7 was considered separately from other strains of *E. coli* (in the intestinal infection disease group) due to differences in mode of transmission, potential interventions for prevention, data sources and magnitude of disease burden.

Data sources and HALY calculation

Because *E. coli* (other than the O157:H7 strain) is not a reportable pathogen, we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes that *E. coli* most commonly causes. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from *E. coli* infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to *E. coli* (to estimate both deaths and incident cases) and the duration of each health state.

Among hospitalized patients, skin and oropharnygeal colonization with gram-negative bacteria such as *E. coli* is very common, and in this context *E. coli* can contribute to a range of other syndromes that would not be common among non-hospitalized patients...

Exhibit 4.4
Parameters for estimating disease burden due to *Escherichia coli* (*E. coli*)

Health State	Percentage of Health State Attributable to *E. coli*	Duration	Severity Weight	Episode Length	Number of Episodes	Number of Deaths
Bacterial meningitis (BM)	7 (0–14 years) 1 (≥15 years)[34, 35]	2 weeks[27]	0.652	3 years	10	0
Sequelae of BM						
Seizures	15[35]	Permanent	0.039	N/A	2	0
Motor deficits	50[35]	Permanent	0.062	N/A	5	0
Deafness	9[36]	Permanent	0.071	N/A	1	0
Septicaemia	23.9[37]	1 week[38]	0.652	30 days	3,723	168
Pneumonia	3.6[48]	2 weeks[27]	0.136	30 days	9,089	70
Acute prostatitis (males only)	3.5 (due to acute infection) 80 (due to E. coli)[49, 50]	1 week[51]	0.039	60 days	1,558	0
Pyelonephritis	80[49]	10 days	0.030	60 days	47,501	362*
Cystitis	80[49]	5 days	0.023	30 days	389,379	

* Deaths due to pyelonephritis and cystitis are aggregated.

Estimated burden

We estimated annual averages of 600 deaths and 451,268 health care utilization episodes attributable to *E. coli*. The burden of *E. coli* was markedly higher in females compared to males, primarily due to a greater number of deaths due to UTIs in older women. Most of the burden of *E. coli* was in individuals aged 65 or older. There were a large number of deaths from UTIs in this age group, with the majority of those deaths (80%) attributable to *E. coli*. A large number of septicaemia deaths attributable to *E. coli* also contributed to the burden in the elderly.

Limitations

These estimates for the burden of *E. coli* are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. *E. coli* is involved in a broader range of syndromes among hospitalized as compared to non-hospitalized patients, but the data used in this study do not adequately distinguish between these sources of acquisition.

4.1.3. *STAPHYLOCOCCUS AUREUS*

S. aureus is a gram-positive bacterium which colonizes the nares (nostrils) of 10–40% of people. The bacterium possesses a range of virulence factors, and although carriage can be asymptomatic, it can also produce a range of serious illnesses. It is the number one pathogen associated with hospital-acquired infections but also a common cause of community-acquired infections. Common sites of infection include cellulitis (soft tissue infection), osteomyelitis (bone infection), septic arthritis (joint infection), septicaemia (bloodstream infection), endocarditis (heart valve infection) and pneumonia (lung infection). Many strains of *S. aureus* now contain genetic material which renders them resistant to penicillin and cephalosporin antibiotics (MRSA, or methicillin resistant *S. aureus*), which further complicates treatment. A vaccine is currently under development.

Data sources and HALY calculation

Because *S. aureus* is not a reportable pathogen, we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes *S. aureus* most commonly causes. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from *S. aureus* infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to *S. aureus* (to estimate both deaths and incident cases) and the duration of each health state.

Exhibit 4.5
Parameters for estimating disease burden due to *Staphylococcus aureus*

Health State	Percentage of Health State Attributable to *Staphylococcus Aureus*	Duration	Severity Weight	Episode Length*	Number of Episodes	Number of Deaths
Septicaemia	15.5[37]	1 week[38]	0.652	30 days	2,415	109
Endocarditis	26[52]	52 days[53]	0.174	60 days	334	46
Pneumonia	3[39]	2 weeks[37]	0.136	30 days	7,574	59
Septic arthritis	37[40]	33 days[41]	0.108	60 days	1,299	6
Cellulitis	50[54]	10.5 days[54]	0.070	30 days	142,293	18
Osteomyelitis	50[55]	6 weeks	0.041	60 days	4,528	30

Estimated burden

We estimated annual averages of 268 deaths and 158,443 health care utilization episodes attributable to *S. aureus*. There was a slightly higher burden of *S. aureus* in females compared to males. Most of the burden due to *S. aureus* is among individuals aged 65 or older, which can likely be attributed to a large number of pneumonia, septicaemia, endocarditis and cellulitis deaths occurring in that age group and a substantial percentage of those deaths being attributed to *S. aureus*.

Limitations

These estimates for the burden of *S. aureus* are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. Due to the lack of comprehensive population-based laboratory data in Ontario, we are unable to determine the fraction of the burden related to MRSA for all sites of infection. However, data from 81 licensed bacteriology laboratories in Ontario indicated that in 2008, 17% (521 of 2,992) of all S. aureus isolated from blood cultures were methicillin resistant, suggesting that roughly one-sixth of the burden of S. aureus may be related to MRSA.[56] While MRSA has received much media attention, the fact that most of the burden from *S. aureus* is still from non-antibiotic resistant strains is underrecognized.

4.1.4. GROUP B STREPTOCOCCUS (*STREPTOCOCCUS AGALACTIAE*)

Group B streptococcus (GBS) is a gram-positive bacterium which can colonize the skin, gastrointestinal tract, as well as the female lower genital tract. Transmission from mother to child can result in neonatal septicaemia (bloodstream infection in the first 28 days of life) and meningitis (cerebrospinal infection). Pregnant mothers can also develop infections of the amniotic fluid or genital tract. The organism also causes invasive infections in non-pregnant adults, especially individuals with underlying diabetes mellitus or cancer. Common sites of invasive infection include cellulitis (soft tissue infection), septicaemia (bloodstream infection), septic arthritis (joint infection) and osteomyelitis (bone infection). Fortunately, GBS remains universally susceptible to penicillin, although some resistance has emerged to other classes of antibiotics. A vaccine is currently under development.

Fortunately, GBS remains universally susceptible to penicillin, although some resistance has emerged to other classes of antibiotics.

Data sources and HALY calculation

GBS is only reportable in neonates, and even among neonates GBS may not be confirmed during the management and treatment of the various syndromes caused by this organism. For these reasons, we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes GBS most commonly causes. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from GBS infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to GBS (to estimate both deaths and incident cases) and the duration of each health state.

Exhibit 4.6
Parameters for estimating disease burden due to Group B streptococcus

Health State	Percentage of Health State Attributable to GBS	Duration	Severity Weight	Episode Length	Number of Episodes	Number of Deaths
Bacterial meningitis (BM)	22 (0–4 years) 6 (5–14 years) 1 (≥15 years)[34, 35]	2 weeks[27]	0.652	3 years	24	1
Sequelae of BM						
Seizures	27 (% of BM cases)[35]	Permanent	0.039	N/A	6	0
Motor deficits	65 (% of BM cases)[35]	Permanent	0.062	N/A	16	0
Deafness	9 (% of BM cases)[36]	Permanent	0.071	N/A	2	0
Septicaemia	1[57, 58]	1 week[38]	0.652	30 days	156	7
Sepsis of newborn (aged 0–1 years)	22.5[59]	1 week[38]	0.652	3 years	334	6
Septic arthritis	10[60, 61]	19 days[41]	0.108	60 days	351	2
Cellulitis	2[61]	10.5 days[54]	0.070	30 days	5,692	1
Osteomyelitis	2[55]	6 weeks	0.041	60 days	183	1

Estimated burden

We estimated annual averages of 18 deaths and 6,764 health care utilization episodes attributable to GBS. The burden of GBS was slightly higher for males because there were more sepsis deaths occurring in neonatal males. Most of the disease burden affected neonates.

Limitations

These estimates for the burden of GBS are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. The distribution of etiologic agents causing neonatal infections is known to be shifting over time (related to changing maternal screening and peripartum prophylaxis strategies in Canada between 1997 and 2004), so our reliance on epidemiologic studies to determine the attributable fraction may lead to overestimates of disease burden.[63]

4.1.5. GROUP A STREPTOCOCCUS (*STREPTOCOCCUS PYOGENES*)

Group A streptococcus (GAS) is a gram-positive bacterium with a human reservoir (throat carriage among 20% of children and a lesser percentage of adults) with person-to-person transmission by respiratory droplets. The bacterium possesses a range of virulence factors, and although carriage can be asymptomatic it can also produce both non-invasive and invasive syndromes. Non-invasive syndromes include pharyngitis (sore throat) and superficial skin infections such as pyoderma or impetigo. Immune-mediated complications can affect the heart through rheumatic fever and kidney via glomerulonephritis. Invasive soft tissue involvement can range from the dermis and subcutaneous tissues as manifested by erysipelas and cellulitis, to rapidly progressive destruction of the deeper fascial layers as manifested by necrotizing fasciitis ("flesh eating" disease). Other common sites of invasive infection include the bone, joint, lung, and bloodstream. Some invasive infections can be accompanied by shock and multi-organ failure as manifested by Streptococcal toxic shock syndrome. Fortunately, GAS remains universally susceptible to penicillin, although some resistance has emerged to other classes of antibiotics. A vaccine is currently under development.

Data sources and HALY calculation

Because GAS is not a reportable disease (aside from invasive infections), we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes GAS most commonly causes. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from GAS infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to GAS (to estimate both deaths and incident cases) and the duration of each health state.

Exhibit 4.7
Parameters for estimating disease burden due to Group A streptococcus

Health State	Percentage of Health State Attributable to GAS	Duration	Severity Weight	Episode Length	Number of Episodes	Number of Deaths
Necrotizing fasciitis	22[64]	8.5 days	0.729	60 days	54	4
Bacterial meningitis	Rare[65]	2 weeks[27]	0.652	3 years	N/A	N/A
Septicaemia	0.6[66]	1 week[38]	0.652	30 days	94	4
Pneumonia	1[67]	2 weeks[27]	0.136	30 days	2,525	20
Septic arthritis	16[40]	19 days[41]	0.108	60 days	562	3
Cellulitis	28.5[54]	10.5 days[54]	0.070	30 days	81,107	17
Pharyngitis	22.5 (% of children) 7.5 (% of adults)[68]	1 week[69]	0.052	30 days	34,647	0

Estimated burden

We estimated annual averages of 48 deaths and 118,989 health care utilization episodes attributable to GAS. The burden of Group A Streptococcus was relatively equal between males and females. The most common manifestation of GAS was pharyngitis, and the majority of these cases occurred in younger individuals. However, the majority of HALYs lost due to GAS were for individuals aged 65 or older. In particular, a large number of cellulitis deaths occurred in that age group, and a high percentage of those deaths are attributed to GAS.

Limitations

These estimates for the burden of GAS are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. Nevertheless, the total number of deaths per year is very similar to the results of Ontario-wide surveillance of invasive group A streptococcal disease that was conducted in this province between 1992 and 2000.[70] We estimated slightly more deaths per year which could be explained by the fact that prior surveillance relied on isolation of the organism from a sterile site culture.

4.1.6. *HAEMOPHILUS INFLUENZAE*

H. influenzae is a gram-negative bacterium with a human reservoir, colonizing the upper airway and female genital tract. The organism is transmitted via respiratory droplets, and can produce infections such as pneumonia (lung infection), septic arthritis (joint infection), epiglottis, septicaemia (bloodstream infection) and meningitis (cerebrospinal fluid infection). The introduction of vaccine against the predominant serotype (serotype b) has led to dramatic reductions in infections with *H. influenzae*, although increases in cases of infections with non-typeable *H. influenzae* have been reported.[71]

Data sources and HALY calculation

Because *H. influenzae* is not a reportable disease (unless it is invasive and serotype b), we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes most commonly cause by *H. influenzae*. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from *H. influenzae* infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to *H. influenzae* (to estimate both deaths and incident cases) and the duration of each health state.

Exhibit 4.8
Parameters for estimating disease burden due to *Haemophilus influenzae*

Health State	Percentage of Health State Attributable to *H. influenzae*	Duration	Severity Weight	Episode Length	Number of Episodes	Number of Deaths
Bacterial meningitis (BM)	4 (0–14 years) 2 (≥15 years)[34, 35]	2 weeks[27]	0.652	3 years	9	0
Sequelae of BM						
Seizures	15 (% of BM cases)[35]	Permanent	0.039	N/A	1	0
Motor deficits	50 (% of BM cases)[35]	Permanent	0.062	N/A	4	0
Deafness	9 (% of BM cases)[36]	Permanent	0.071	N/A	1	0
Septicaemia	0.4[72]	1 week[38]	0.652	30 days	62	3
Pneumonia	3[73]	2 weeks[27]	0.136	30 days	7,754	59
Septic arthritis	1[40]	19 days[41]	0.108	60 days	35	0
Otitis media	13[44]	4.5 days[45]	0.052	30 days	97,210	0

Estimated burden

We estimated annual averages of 62 deaths and 105,076 health care utilization episodes attributable to *H. influenzae*. The burden of *H. influenzae* was relatively equal between males and females. Since the majority of deaths attributed to *H. influenzae* were due to pneumonia and most pneumonia deaths occur in older individuals, most of the burden was in individuals aged 65 or older.

Limitations

These estimates for the burden of *H. influenzae* are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. The distribution of etiologic agents causing many of the infectious syndromes caused by *H. influenzae* is known to be shifting over time (due to universal immunization against *H. influenzae* type b), so our reliance on epidemiologic studies to determine the attributable fraction may lead to invalid estimates of disease burden. The assumption that the attributable fraction of the included syndromes for *H. influenzae* is the same for non-fatal and fatal cases would likely lead to an overestimate of *H. influenzae* burden, because this pathogen is generally less virulent than other leading causes of meningitis. Additionally, epiglottitis was not considered as a health state in this analysis because a suitable etiologic study in the post *H. influenzae* type B vaccination era could not be found. This omission could lead to an underestimate of *H. influenzae* burden.

4.1.7. *LEGIONELLA*

Legionella is a gram-negative bacterium that is responsible for Pontiac fever and Legionnaire's disease. It acquired its name in 1976 after an outbreak that occurred at a war veteran convention of the American Legion. It is found in freshwater ponds, cooling towers, swimming pools, air conditioning systems and fountains. It is not spread from person-to-person, but through mist droplets from its water sources. After an incubation period of two to 10 days, patients with Legionnaire's disease may experience fevers, chills, cough and ataxia (loss of coordination) and may also exhibit gastrointestinal symptoms, such as vomiting or diarrhea. Mortality occurs from pneumonia and has been as high as 30% in previous outbreaks. Antibiotics are the treatment of choice for *Legionella* pneumonia. Pontiac fever has the same initial symptoms as Legionnaire's disease but is not associated with pneumonia or death. Public water systems are routinely tested for *Legionella*, and bacterial levels are controlled through chlorination among other methods.

Data sources and HALY calculation

Legionella is rarely confirmed with laboratory testing because most cases of pneumonia are treated empirically without identifying the causative pathogen. Therefore, analyzing only reported cases of legionellosis would severely underestimate the burden of *Legionella*. Consequently, we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes *Legionella* most commonly causes. For YERF, we used Ontario health care utilization data to determine the number of episodes of pneumonia. We used epidemiologic studies to determine the percentage of pneumonia attributable to *Legionella* and the duration of pneumonia.

Exhibit 4.9
Parameters for estimating disease burden due to *Legionella*

Health State	Percentage of Health State Attributable to *Legionella*	Duration	Severity Weight	Episode Length	Number of Episodes	Number of Deaths
Pneumonia	3[39]	2 weeks[27]	0.136	30 days	7,574	59

Estimated burden
We estimated annual averages of 59 deaths and 7,574 health care utilization episodes (all pneumonia) attributable to *Legionella*. The burden of *Legionella* was relatively equal between males and females. Since pneumonia was the only health state considered for *Legionella* and most pneumonia deaths occur in older individuals, most of the burden from *Legionella* was in individuals aged 65 or older.

Limitations
These estimates for the burden of *Legionella* are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. Use of epidemiologic studies to determine the attributable fraction is a particular concern for *Legionella* because that there are wide geographic and temporal variations in this proportion which are not well understood (apart from outbreaks). The assumption that *Legionella* is responsible for the same attributable fraction of pneumonia mortality and incidence would likely lead to an underestimate of *Legionella* burden. This pathogen is generally more virulent than other leading causes of pneumonia.

4.1.8. *NEISSERIA MENINGITIDIS*

N. meningitidis (meningococcus) is a gram-negative bacterium with a human reservoir, colonizing a variable proportion of healthy people. New strains are acquired by respiratory droplets, and occasionally result in severe invasive illnesses. The most common presentations are septicaemia or meningococcemia (bloodstream infections) which can be fulminant and rapidly fatal, as well as meningitis (cerebrospinal fluid infection). Most cases are sporadic, but some are associated with outbreaks. The organism is usually susceptible to penicillin or cephalosporin antibiotics. Prophylactic antibiotics are also offered to close contacts of infected patients, and vaccines are now available for some serogroups (A, C, Y and W135). There is no vaccine against serogroup B.

Data sources and HALY calculation

We used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes *N. meningitidis* most commonly causes. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from *N. meningitidis* infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to *N. meningitidis* (to estimate both deaths and incident cases) and the duration of each health state. However, we were unable to accurately identify the fraction of septicaemia cases attributable to *N. meningitidis* (since only a negligible proportion of bacteremia episodes are caused by this pathogen), so did not include that as a health state. As a comparison, we also examined the number of reported cases of invasive meningococcal infection in the Ontario reportable disease dataset (iPHIS). Unfortunately, we did not have access to the data to differentiate between meningitis and septicaemia.

Most cases are sporadic, but some are associated with outbreaks. The organism is usually susceptible to penicillin or cephalosporin antibiotics.

Exhibit 4.10
Parameters for estimating disease burden due to *Neisseria meningitidis*

Health State	Percentage of Health State Attributable to *N. meningitidis*	Duration	Severity Weight	Episode Length	Number of Episodes	Number of Deaths
Bacterial meningitis (BM)	25 (0–4 years) 35 (5–14 years) 37 (≥15 years)[34, 35]	2 weeks [27]	0.652	3 years	108	7
Sequelae of BM						
Seizures	5 (% of BM cases)[35]	Permanent	0.039	N/A	5	0
Motor deficits	33 (% of BM cases)[35]	Permanent	0.062	N/A	36	0
Deafness	9 (% of BM cases)[36]	Permanent	0.071	N/A	10	0

Estimated burden

We estimated annual averages of seven deaths and 159 health care utilization episodes attributable to *N. meningitidis*. The burden was relatively equal between males and females. Bacterial meningitis was the most prominent health state caused by *N. meningitidis*, and most of the burden occurred in children aged 0–14 years.

There was an average of 72 cases per year of invasive meningococcal disease recorded in iPHIS (i.e., reported to public health authorities). Using the syndrome-based approach, we estimated 108 meningococcal meningitis episodes per year.

Limitations

These estimates for the burden of *N. meningitidis* are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. The omission of meningococcal septicaemia as a health state could lead to an underestimation of the burden of illness secondary to meningococcal disease in Ontario; however, given the rarity of the outcome, this underestimation is likely to be small. Our methodology does not capture changing disease incidence over time, and there is some evidence from other jurisdictions in North America that meningococcal disease has been decreasing over the past decade—not unexpected given implementation of universal meningococcal vaccination programs during the time period under study.[74]

4.1.9. OTHER GRAM-NEGATIVE BACTERIA

Although *E. coli* is the most common gram-negative bacterium to produce clinical illness, and the burden of some other gram-negative bacteria are considered separately (*Legionella*, *Haemophilus influenzae* type B), there are a number of other gram-negative bacilli commonly implicated in infections (*Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., *Citrobacter* spp., *Pseudomonas* spp., *Serratia* spp., *Acinetobacter* spp., etc.). The spectrum of illnesses caused by these pathogens is relatively similar to those described for *E. coli*.

Data sources and HALY calculation

Because infections with these bacteria are not reportable we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes these bacteria most commonly cause. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from other gram-negative bacterial infections. We used epidemiologic studies to determine the percentage of each syndrome attributable to other gram-negative bacteria (to estimate both deaths and incident cases) and the duration of each health state.

Exhibit 4.11
Parameters for estimating disease burden due to other gram-negative bacteria

Health State	Percentage of Health State Attributable to Other Gram-Negative Bacteria	Duration	Severity Weight	Episode Length	Number of Episodes	Number of Deaths
Bacterial meningitis (BM)	3 (0–14 years); 1 (≥15 years)[34, 35]	2 weeks[27]	0.652	3 years	6	0
Sequelae of BM						
Seizures	15 (% of BM cases)[35]	Permanent	0.039	N/A	1	0
Motor deficits	50 (% of BM cases)[35]	Permanent	0.062	N/A	3	0
Deafness	9 (% of BM cases)[36]	Permanent	0.071	N/A	1	0
Septicaemia	22.136	1 week[38]	0.652	30 days	3,443	155
Endocarditis	274	57 days[53]	0.174	60 days	26	4
Pneumonia	1047	2 weeks[27]	0.136	30 days	265,247	195
Acute prostatitis (males only)	3.5 (% of prostatitis due to acute infection); 10 (% of acute prostatitis due to other gram-negative bacteria)[49, 50]	1 week[51]	0.039	60 days	195	0
Pyelonephritis	10[49]	10 days	0.03	60 days	5,938	45*
Cystitis	10[49]	5 days	0.023	30 days	48,672	

* Deaths due to pyelonephritis and cystitis were aggregated.

Estimated burden

We estimated annual averages of 400 deaths and 83,532 health care utilization episodes attributable to other gram-negative bacteria. The burden of other gram-negative bacteria was higher in females compared to males, primarily due to a higher number of deaths due to UTIs in females. Most of the burden of other gram-negative bacteria affects individuals aged 65 or older, which can likely be attributed to a large number of deaths due to urinary tract infection in this age group. A large number of septicaemia and pneumonia deaths attributable to other gram-negative bacteria also contribute to the burden of these infectious agents in the elderly.

Limitations

These estimates for the burden of other gram-negative bacteria are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. Due to the lack of comprehensive laboratory data, we are unable to determine the fraction of the burden related to drug-resistant gram-negative bacteria. This group of pathogens highlights another important limitation of our methodology: we have not distinguished community-acquired infections from hospital-acquired infections. For example, some of these organisms (e.g., *Pseudomonas*) are among the top causes of hospital-acquired pneumonia but only rare causes of community-acquired pneumonia.

4.1.10. OTHER GRAM-POSITIVE BACTERIA

In addition to the leading gram-positive bacterial pathogens, which have been described separately (*S. pneumoniae*, *S. aureus*, group A streptococcus, group B streptococcus), there are a number of other important organisms in this category that we have grouped together for the purpose of this analysis (*Enterococcus*, *Streptococcus viridans*, non-group A non-group B beta-hemolytic streptococci, coagulase-negative staphylococci and others). These organisms are heterogeneous with respect to their clinical manifestations but are common contributors to a number of different syndromes, such as endocarditis, genitourinary infections, septic arthritis and septicaemia.

Data sources and HALY calculation

As other gram-positive bacteria are not always confirmed with laboratory testing and infection with these bacteria are not reportable, we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes other gram-positive bacteria most commonly cause. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from other gram-positive bacterial infections. We used epidemiologic studies to determine the percentage of each syndrome attributable to other gram-positive bacteria (to estimate both deaths and incident cases) and the duration of each health state.

Exhibit 4.12
Parameters for estimating disease burden due to other gram-positive bacteria

Health State	Percentage of Health State Attributable to Other Gram-Positive Bacterial Infections	Duration	Severity Weight	Episode Length	Number of Episodes	Number of Deaths
Septicaemia	24.5[57]	1 week[38]	0.652	30 days	3,817	172
Endocarditis	42[76]	52 days[53]	0.174	60 days	539	74
Septic arthritis	5[40]	19 days[41]	0.108	60 days	176	1
Acute prostatitis (males only)	3.5 (% due to acute infection); 3.8 (% due to other gram-positive bacteria)[50, 77]	1 week[51]	0.039	60 days	74	0
Pyelonephritis	3.8[77]	10 days	0.030	60 days	2,256	17*
Cystitis	3.8[77]	5 days	0.023	30 days	18,496	

* Deaths due to pyelonephritis and cystitis are aggregated.

Estimated burden

We estimated annual averages of 264 deaths and 25,358 health care utilization episodes attributable to other gram-positive bacteria. The burden of other gram-positive bacteria was similar in both males and females. Most of the burden due to other gram-positive bacteria was in those aged 65 or older, likely because of a large number of deaths due to septicaemia and endocarditis in this age group.

Limitations

These estimates for the burden of other gram-positive bacteria are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. This is especially true given that a different profile of gram-positive pathogens contribute to each of the above syndromes. For example, *Streptococcus viridans* is a common cause of endocarditis but not cystitis; *Staphylococcus saprophyticus* is a common cause of cystitis but not endocarditis; *Enterococcus* is a common cause of both of these syndromes.

4.2 VIRAL HEPATITIS

All major types of viral hepatitis (hepatitis A, B and C) were considered to this disease group. Viral hepatitis is characterized by inflammation of the liver and may have both asymptomatic (subclinical) and symptomatic phases. Hepatitis A is distinct from B and C in terms of route of transmission, prognosis and epidemiology. It causes only acute viral hepatitis; hepatitis B and C may cause both acute and chronic viral hepatitis. Since hepatitis A burden is primarily related to acute illness, and hepatitis B and C burden is mostly related to chronic illness and complications, different approaches are required to calculate the disease burden for the respective strains.

Within this disease group, hepatitis C was found to have the highest disease burden in Ontario, with nearly twice the burden of hepatitis B (Exhibit 4.13). The burden of hepatitis A was negligible. For both hepatitis B and C, disease burden was much higher in males, although the relative magnitude of the difference in burden between males and females was greater for hepatitis B (Exhibit 4.14).

Exhibit 4.13

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for common bacterial infections

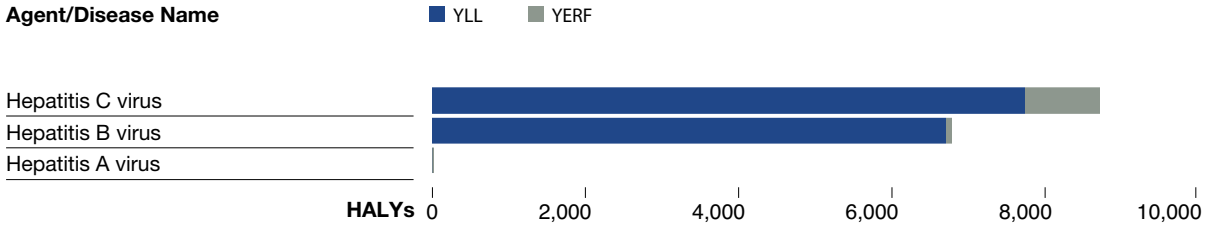
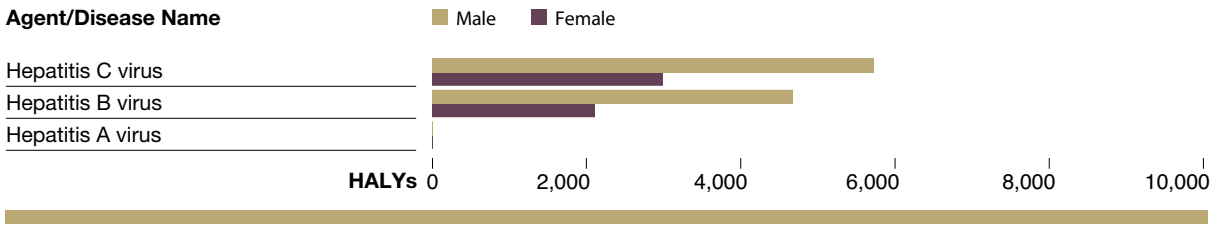


Exhibit 4.14

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for common bacterial infections, by sex



4.2.1. HEPATITIS C VIRUS

Hepatitis C virus (HCV) infects the liver, and is most commonly transmitted by blood to blood contact, such as sharing contaminated needles. After an incubation period of several weeks, most people are asymptomatic; however the majority (50–85%) of infected people eventually develop chronic hepatitis. Cirrhosis (liver scarring and loss of function) is common over time (4–10% after 20 years),[78] and some patients develop hepatocellular carcinoma (liver cancer) (1–3% after 30 years).[79] The infection can be cleared by antiviral medications; however hepatitis C remains the most common cause for liver transplants. There are no vaccines available against HCV.

Data sources and HALY calculation

Although HCV is a reportable disease in Ontario, reported cases generally represent infections that occurred in the past. In addition, diagnosis is difficult due to the presence of only mild or non-specific symptoms and/or the failure of physicians to consider HCV and order the appropriate diagnostic testing.

For YLL, we used Ontario vital statistics data to estimate deaths related to hepatitis C. We included 100% of deaths coded as hepatitis C, 25% of deaths coded as hepatocellular cancer (personal communication, Dr. Morris Sherman, March 5, 2010) and 27% of deaths coded as unspecified cirrhosis or hepatic failure (hepatic failure, chronic hepatitis, other and unspecified cirrhosis, portal hypertension, hepatorenal syndrome and esophageal varices).[80] The latter two were necessary because HCV infection is frequently underdiagnosed and underreported.

For YERF, we used the results of an actuarial model to estimate the incidence of new infections of HCV and projected outcomes of chronic HCV infection. Details of this model are described elsewhere.[81] The investigators first estimated the populations potentially at risk for HCV infection, stratifying the population by country of birth (Canadian-born vs. immigrants) and risk group (injection drug users, blood transfusion recipients, hemophilia patients and the general population) and taking into account life table mortality and deaths from competing causes (e.g., HIV, drug use, trauma). Next, HCV incidence for each group was modeled from various data sources, while adjusting for underreporting and asymptomatic infection. Lastly, the investigators used published transition parameters and a Markov model to estimate the incidence and durations of outcomes experienced by HCV-infected individuals over time (chronic hepatitis, decompensated cirrhosis, hepatocellular cancer and liver transplant).

Exhibit 4.15
Parameters for estimating the disease burden due to hepatitis C virus

Health State	Duration*	Severity Weight	Number of Cases Expected to Develop Health State
Chronic hepatitis	7.5 years	0.035	358
Decompensated cirrhosis	5.8 years	0.628	216
Hepatocellular cancer	0.58 years	0.357	135
Transplant	7.1 years	0.057	61

* Median duration for all ages and sexes combined.

...hepatitis C remains the most common cause for liver transplants. There are no vaccines available against HCV.

Estimated burden

We estimated annual averages of 369 deaths from HCV (144 coded as hepatitis C, 66 coded as hepatocellular cancer and 153 coded as unspecified cirrhosis or hepatic failure) and 3,469 incident cases of HCV infection. The burden of HCV was greatest among men aged 44–50 years.

Limitations

These estimates for the burden of HCV are limited most significantly by uncertainty around attributing non-specific liver-related deaths to HCV. In our calculation of YLL, we included 100% of deaths coded as "hepatitis C" under the assumption that all such deaths are truly due to HCV. We then included 25% of deaths coded as hepatocellular cancer based on data from the largest quaternary care centre in Ontario.[82] However, that proportion may not be representative of the entire province. Interestingly, that proportion matched precisely data from a global liver cancer and primary cirrhosis study.[80] Lastly, we also included 27% of deaths coded as one of several non-specific liver-related conditions (listed above) based on data from the same global study. Again, these data might not generalize to the experience in Ontario and may have resulted in an over-estimation of the burden of illness, as their inclusion resulted in 41% of the total HCV-attributable deaths. Although we suspect that some proportion of HCV-related deaths are not coded as such, we are uncertain about the precise extent of underdiagnosis and undercoding of HCV-related deaths; the inclusion of non-specific liver-related conditions would have minimized this. Since YLL accounted for most of the burden of HCV, we may have over- or underestimated the true burden of HCV. For example, not including any of the deaths coded as one of the non-specific conditions would decrease the burden of HCV from 9,658 to 6,377 HALYs, which would still keep HCV among the four most burdensome pathogens. Another limitation of these estimates is that the mortality burden derived from current vital statistics data may not represent the future mortality burden resulting from current incident cases, as therapies such as entecavir and tenofovir have recently been used to successfully treat patients with HCV and others might be available in the future. Finally, we did not consider the decrease in quality of life resulting from treatment/remission for liver cancer because the average survival time for liver cancer is generally quite short.

4.2.2. HEPATITIS B VIRUS

Hepatitis B virus (HBV) infects the liver, and is transmitted by sexual contact, injection drug use, and vertical transmission from mother-to-child during delivery. After an incubation period of one to four months, infection can be asymptomatic or can result in acute hepatitis (liver inflammation) with symptoms such as fever, weight loss, abdominal pain, fatigue and jaundice. The majority of infected infants (80–90%) go on to develop chronic hepatitis, but only a minority of infected adults (5%) do so. Chronic hepatitis can be complicated by cirrhosis (liver scarring and loss of function), as well as hepatocellular carcinoma (liver cancer). Antiviral medications can be used to slow the infection, and a vaccine is available to protect against infection.

Data sources and HALY calculation

Although HBV is a reportable disease in Ontario, reported cases represent acute infections due to the case definition used for surveillance;[83] persons with chronic hepatitis B infection would be omitted. In addition, the disease may be underdiagnosed due to the presence of only mild or non-specific symptoms, the failure of individuals to present for testing, and/or the failure of physicians to consider HBV and order the appropriate diagnostic testing.

For YLL, we used Ontario vital statistics data to estimate deaths related to hepatitis B. We included 100% of deaths coded as hepatitis B, 55% of deaths coded as hepatocellular cancer, (personal communication, Dr. Morris Sherman, March 5, 2010), and 30% of deaths coded as cirrhosis or hepatic failure (hepatic failure, chronic hepatitis, other and unspecified cirrhosis, portal hypertension, hepatorenal syndrome and esophageal varices).[80] The latter two were necessary because HBV infection is frequently underdiagnosed and underreported.

For YERF, we estimated the incidence of new HBV infections using estimates from the Public Health Agency of Canada's Enhanced Hepatitis Sentinel Surveillance System (EHSSS), adjusting for asymptomatic new infections,[84] underreporting and the high specificity of the EHSSS case definition. (personal communication, Dr. Robert Remis, August 20, 2009). We used epidemiologic studies to estimate the outcomes experienced by HBV-infected individuals over time (acute symptomatic episode, chronic hepatitis, decompensated cirrhosis, hepatocellular cancer and liver transplant).

Exhibit 4.16
Parameters for estimating the disease burden due to hepatitis B virus

Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Acute symptomatic episode	6 weeks	0.121	65
Chronic hepatitis	12 years	0.035	12
Decompensated cirrhosis	21 months	0.628	13
Hepatocellular cancer	0.58 years	0.357	308
Transplant	7.1 years	0.057	4

Estimated burden

We estimated annual averages of 346 deaths (32 coded as hepatitis B, 145 coded as hepatocellular cancer, and 170 coded as unspecified cirrhosis or hepatic failure) and 213 incident cases of HBV infection. Most of the disease burden affects males and individuals between the ages of 40 and 79.

Limitations

These estimates for the burden of HBV are limited most significantly by uncertainty around attributing non-specific liver-related deaths to HBV. In our calculation of YLL, we included 100% of deaths coded as "hepatitis B" under the assumption that all such deaths are truly due to HBV. We then included 55% of deaths coded as hepatocellular cancer based on data from the largest quaternary care centre in Ontario.[82] However, that proportion may not be representative of the entire province. Interestingly, that proportion very closely matched data from a global liver cancer and primary cirrhosis study (the proportion was 53% in that study).[80] Lastly, we also included 30% of deaths coded as one of several non-specific liver-related conditions (listed above) based on data from the same global study Again, these data might not generalize to the experience in Ontario and may have resulted in an over-estimation of the burden of illness, as their inclusion resulted in 49% of the total HBV-attributable deaths.

Although we suspect that some HBV-related deaths are not coded as such, we are uncertain about the extent of underdiagnosis and undercoding of HBV-related deaths; the inclusion of non-specific liver-related conditions would have minimized this. Since YLL accounted for most of the burden of HBV, we may have over- or underestimated the true burden of HBV. For example, not including any of the deaths coded as one of the non-specific conditions would decrease the burden of HBV from 6,704 to 3,479 HALYs.

Another limitation of these estimates is that the mortality burden derived from current vital statistics data may not represent the future mortality burden resulting from current incident cases, as therapies such as entecavir and tenofovir have recently been used to successfully treat patients with HBV and others might be available in the future. We are fairly certain that our estimate of YERF is an underestimate because we based it on new infections that have occurred in Ontario as derived from surveillance data. However, most patients with HBV in Ontario originate from HBV-endemic regions and acquired their infection prior to immigration,[85] and our methodology did not capture those cases of HBV-related illness. Nonetheless, our estimate of the mortality burden includes the deaths occurring among this population. Finally, we did not consider the decrease in quality of life resulting from treatment/remission for liver cancer because the average survival time for liver cancer is generally quite short.

4.2.3. HEPATITIS A VIRUS

Hepatitis A virus (HAV) infects the liver and is transmitted by contaminated food and water sources. Canadians most often acquire the infection during travel to endemic countries. High-risk groups include those living in poverty and Aboriginal populations. In recent years, outbreaks have been reported in specific risk groups: children, men who have sex with men, homeless populations and injecting drug users. After an incubation period of about a month, it can cause hepatitis (liver inflammation) with symptoms such as fever, weight loss, abdominal pain, fatigue and jaundice. Fewer than 5% develop fulminant hepatitis, and the case fatality ratio is 0.5% overall but varies greatly with age. Treatment is generally supportive, although liver transplantation may be required in rare cases of hepatic failure. A highly effective vaccine is available that provides protection from the virus; however, the vaccine is currently not publicly funded in Ontario unless the individual is a member of a high-risk group (persons with chronic liver disease, persons engaging in intravenous drug use and men who have sex with men). The vaccine is also available for purchase among persons who travel to high-risk countries.

Data sources and HALY calculation

Since hepatitis A is a reportable disease in Ontario, we used an agent-based approach to calculate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to hepatitis A infection. For YERF, we extracted reported cases of hepatitis A from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute, uncomplicated episode of hepatitis A. Since reported cases may underestimate the actual number of cases in the community, we used epidemiologic studies to quantify the underreporting of hepatitis A.[86, 87] Using data from these papers, we estimated there were five hepatitis A cases in the community for every case that was diagnosed and reported. We used epidemiologic studies to determine the percentage of reported hepatitis A cases that progressed to a prolonged/relapsing episode or required a transplant and to determine the duration of illness of each of these health states. A mathematical model was used to estimate survival time after transplantation to determine duration.

Exhibit 4.17
Parameters for estimating the disease burden due to hepatitis A virus

Health State	Percentage of Reported Hepatitis A Cases per Year that Progress to Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Acute uncomplicated episode of hepatitis A	100	1.5 weeks[28]	0.121	795
Prolonged episode of hepatitis A	15[88]	1 year[28]	0.136	119
Liver transplant	1[88]	Modeled estimates based on survival time after transplantation	0.057	8

Estimated burden

We estimated annual averages of 0 deaths and 795 incident cases attributable to hepatitis A. Since there were no deaths due to hepatitis A, the entire disease burden was a result of YERF. The disease burden attributed to hepatitis A is relatively similar between males and females and mostly affects individuals between the ages of one and 44.

Limitations

A major limitation of these estimates of HAV disease burden is the high likelihood of underdiagnosis and underreporting. We adjusted for underreporting based on studies conducted in the United States and Australia; however, those results may not be generalizeable to Ontario. The validity of these estimates is also dependent on the quality of the reportable disease data. The limitations of these data are described in greater detail in Chapter 5.

4.3 SEXUALLY TRANSMITTED INFECTIONS (STIS)

Infectious agents assigned to this disease group are most frequently spread through sexual contact. These diseases were associated with a diverse set of health states as some infections are associated with genital lesions (herpes) or with inflammation of the cervix or urethra (chlamydia and gonorrhea), while infection with human papillomavirus (HPV) is the main cause of malignancies in the anogenital region (cervix, vagina, vulva, penis, anal canal), as well as genital warts. Some of the pathogens in the STI disease group are reportable (HIV, syphilis, chlamydia and gonorrhea), and some have clearly definable syndromes that could be captured using health care utilization data. The incidence of some other pathogens could not be quantified using either reported cases or health care utilization data, so estimates of incidence from epidemiologic studies or from mathematical models were used instead.

Within this disease group, HPV was calculated to have the highest disease burden (Exhibit 4.18). The next most closely ranked pathogen was HIV/AIDS. The dominance of HPV in this disease group is attributable to the burden from HPV-related cancer incidence and mortality in young women. Most of the disease burden attributed to STIs was found in females, as HPV, gonorrhea and chlamydia all had much higher disease burden in females compared with males (Exhibit 4.19). However, this is in direct contrast to the burden of HIV/AIDS in Ontario, which is far greater in males than females.

Exhibit 4.18

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for sexually transmitted infections

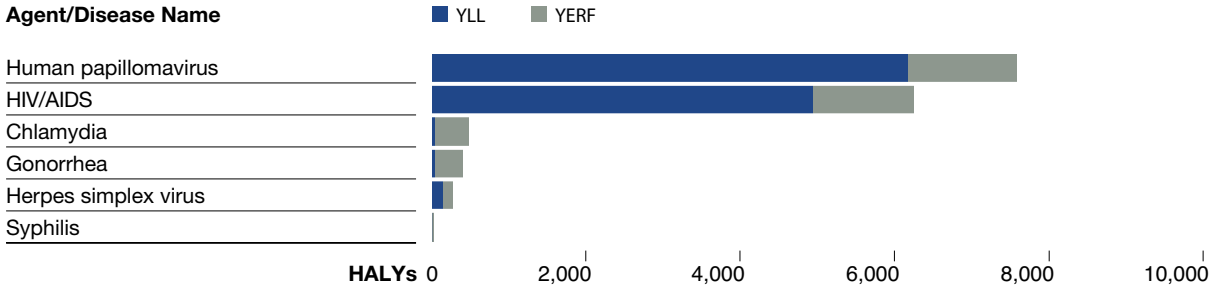
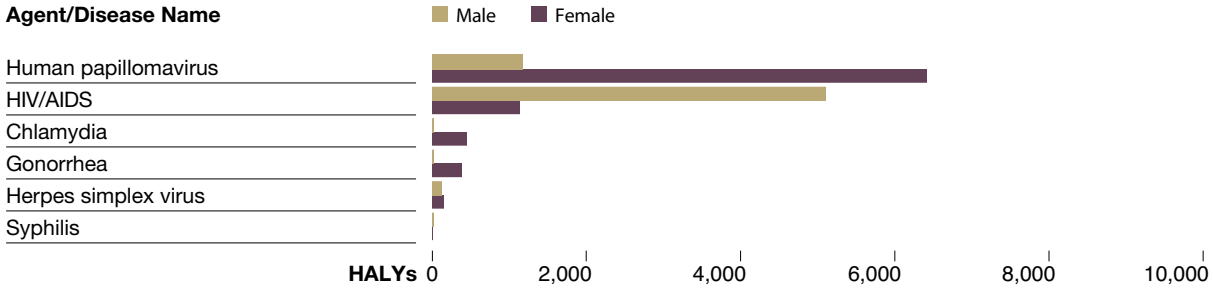


Exhibit 4.19

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for sexually transmitted infections, by sex



4.3.1. HUMAN PAPILLOMAVIRUS

Human papillomavirus (HPV) is transmitted through sexual contact and is the leading cause of cervical cancer, anal cancer and genital warts. Most infections resolve spontaneously in women who are otherwise healthy; infections are typically asymptomatic. HPV is capable of causing benign and cancerous anogenital disease, as well as benign and malignant head and neck lesions.[89] Studies over the past two decades have revealed that persistent infection with oncogenic HPV types is the necessary cause of virtually all cervical cancer. In efforts to reduce the morbidity and mortality related to cervical cancer, pap smears are routinely used to screen for abnormal cells that may lead to cervical cancer. Vaccines are available to prevent two of the oncogenic forms of HPV; one vaccine also protects against non-oncogenic forms of HPV, which are responsible for about 90% of genital warts.

Data sources and HALY calculation

Since HPV is not a reportable disease in Ontario, we used a syndrome-based approach to calculate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to the following malignancies (syndromes) caused by HPV: cancer of the cervix, vulva, vagina, anal canal, penis and oropharynx. For YERF, the Ontario Cancer Registry (OCR) was used to determine incident cases of the malignancies listed above. We used epidemiologic studies to determine the percentage of each cancer attributable to HPV (to estimate both deaths and incident cases).

To calculate YERF for the HPV-related cancers, we adapted the approach developed by Statistics Canada for estimating the burden of cancers.[90] Briefly, individuals with cancer experience some or all of the following health states: diagnosis (good, fair or poor prognosis), treatment (surgery, radiation, chemotherapy and certain combinations of those options), remission (after one or more treatment modalities), and if death occurs within five years, palliative care and terminal care (last month of life) attributable to the cancer. Stage distributions at diagnosis (i.e., proportion of individuals diagnosed at a particular stage) were obtained from the OCR for 2007 and 2008. Five-year relative survival estimates and treatment distributions were determined from epidemiologic studies and expert opinion.

We made several simplifying assumptions. The first was that all incident cases underwent some form of treatment. In reality, some patients are too frail at diagnosis to receive treatment, but the proportion not undergoing any treatment is generally small. Second, we simplified the treatment options by not distinguishing between curative and palliative radiation therapy and by not considering chemotherapy associated with mild, moderate and severe toxicity (keeping the mild form only). Third, we assumed that only the deaths that occurred within five years of diagnosis were attributable to the cancer (i.e., those who survived past five years died of something else), and those who survived past five years had a life expectancy that was the same as the rest of their age-sex stratum. Fourth, we assumed that the proportion dying within five years was independent of the type(s) of treatment and that those who died experienced on average 2.25 years in remission (five years minus the time spent in palliative (five months) and terminal care (one month) divided by two = 4.5 years/2 = 2.25 years). Fifth, we assumed the reduction in functioning to be similar when in remission, regardless of the treatment modality (or modalities) employed. Finally, we did not consider recurrent cancers.

The results of a study from Manitoba were used to estimate the age- and sex-specific incidence rates of anogenital warts.[91]

Exhibit 4.20
Parameters for estimating disease burden due to human papillomavirus (HPV)-related cancers

Cancer site	Percentage Attributed to HPV	Stage	Percentage at Diagnosis	Severity Weight for Diagnosis^	Five-Year Survival	Surgery Only	Radiation Only	Surgery & Radiation	Chemotherapy & Radiation	Surgery, Chemotherapy & Radiation
Cervix	99.7[92]	I	52	0.109	80[27]	60*			25	15
		II	21	0.147	65				100	
		III/IV	27	0.191	30		10		90	
Vulva	36–40[93]	I/II	66	0.109	85	80*			10	10
		III/IV	34	0.191	25	35			50	15
Vagina	90[93]	All	100	0.147	54[94]		10*		90	
Anal canal	85[93]	I/II	56	0.109	80**		5**	95		
		III/IV	44	0.147	55		5	85		10
Penis	50[27]	All	100	0.109	85	100				
Oropharynx	33–72[93]	I/II	18	0.109	85[95, 96]		100***			
		III/IV	82	0.147	70		40		60	

Note: for ranges, the midpoint was used in estimates
^ Dependent on prognosis (i.e., five-year survival)

* Personal communication. Dr. Joan Murphy, University Health Network, Toronto, Canada

** Personal communication. Dr. Bernard Cummings, University Health Network, Toronto, Canada

*** Personal communication. Dr. Ian Poon, Sunnybrook Health Sciences Centre, Toronto, Canada

Exhibit 4.21
Parameters for estimating the disease burden of various health states of human papillomavirus (HPV)

Health State	Severity Weight	Duration
Surgery	0.268	4 weeks
Radiation	0.219	6 weeks
Chemotherapy	0.250	2 weeks
Remission	0.035	Lifetime
Palliative care	0.516	5 months
Terminal care	0.821	1 month

Estimated burden

We estimated annual averages of 254 deaths (157 from cervical cancer, 12 from vaginal cancer, 19 from vulvar cancer, 24 from anal canal cancer, 5 from penile cancer and 37 from oropharyngeal cancer), 1,090 incident malignancies (528 cases of cervical cancer, 45 cases of vaginal cancer, 67 cases of vulvar cancer, 219 cases of anal canal cancer, 25 cases of penile cancer and 206 cases of oropharyngeal cancer) and 14,666 incident cases of anogenital warts attributable to HPV. The burden of HPV was significantly higher in females as there were many more incident cases of cancer and cancer deaths in females. Disease burden attributable to HPV affects individuals over the age of 20 years with the burden peaking in those aged 40–64.

Limitations

Most of the limitations have been outlined in the simplifying assumptions in the Data Sources and HALY Calculation section. In addition, the wide range of estimates in the percentage of oropharyngeal cancers attributable to HPV is evidence of the uncertainty associated with this parameter and may have lead to either an under- or overestimation of the burden of illness. Data regarding the etiology of oropharyngeal cancers are emerging and more precise estimates will likely be available in the future. Another limitation is the assumption that HPV is responsible for the same attributable fraction for both cancer mortality and incidence. However, this may not be the case. For example, patients with HPV-positive oropharyngeal cancers have a better prognosis than those with HPV-negative cancers.[97] Finally, recurrent respiratory papillomatosis (juvenile or adult onset) was not included in this study, leading to an underestimate of the burden of HPV. Although relatively rare (prevalence estimated at one per 100,000 children), this condition can cause substantial morbidity in affected individuals.[98]

4.3.2. HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNODEFICIENCY SYNDROME

Human immunodeficiency virus (HIV), the virus associated with Acquired immunodeficiency syndrome (AIDS), was first discovered in 1983, had caused more than 25 million deaths by 2006, and currently infects more than 40 million people worldwide. The virus is transmitted by sexual contact, use of needles contaminated with HIV, exposure to HIV-infected bodily fluids, and from mother to child via the birth canal or breastfeeding. It infects human white blood cells and gradually destroys the immune system, so that after a prolonged latent period, patients eventually develop "opportunistic" infections. If untreated, HIV infection progresses to death after a median of 10 years. There is currently no cure for HIV, but a combination of antiviral medications can suppress the virus, allowing patients to survive for a much longer (and as of yet undefined) time.

Data sources and HALY calculation

Although HIV and AIDS are reportable diseases in Ontario, reported cases include a mixture of both incident and prevalent cases of infection, as the period between infection and laboratory confirmation varies among all reported cases of HIV/AIDS. For YLL, we used Ontario vital statistics data to determine the number of deaths due to HIV. For YERF, we calculated the disease burden due to HIV and AIDS separately. For HIV, we used the results of a mathematical model to estimate the incidence of new infections of HIV for the years 2005–2007. To calculate HIV incidence, HIV serodiagnoses among different HIV exposure categories (men who have sex with men, injection drug use, mother-to-child transmission, blood product/transfusion recipient, emigrated from HIV-endemic area, heterosexual transmission) from the Ontario Central Public Health Laboratory were extracted. Results from detuned assays were used to distinguish between recent and remote HIV infection, and data from different HIV/AIDS studies were used to adjust for selection biases associated with HIV testing patterns among individuals at varying risks to HIV and HIV incidence among repeat testers, as well as determine the exposure category for those with missing risk factor information.[99] The incidence among the different exposure groups was aggregated to yield a total number of cases for Ontario. The above mathematical model also produced estimates of AIDS incidence by using reported AIDS cases from the Ontario AIDS Surveillance Program and adjusting for reporting delays and underreporting.[99] A simplifying assumption was that all cases of AIDS would reach the terminal phase of AIDS, although it is possible that some individuals with AIDS may have died from other causes before the terminal phase. Durations of HIV and AIDS were determined using modeled survival times.

Exhibit 4.22

Parameters for estimating the disease burden due to human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)

Health State	Duration (years)	Severity Weight	Number of Cases Expected to Develop Health State
HIV	20	0.035	1,659
AIDS	1.7	0.247	306
AIDS – terminal phase	0.08	0.801	306

Estimated burden

We estimated annual averages of 133 deaths due to HIV/AIDS and 1,659 incident cases of HIV, as well as 306 cases of AIDS. Most of the burden due to HIV/AIDS was from YLL. HIV/AIDS burden was significantly higher in males, and most of the burden was in those aged 30–59.

Limitations

These estimates for the burden of HIV/AIDS are limited by the uncertainty arising from only having a single underlying cause of death available in the mortality data available for this study. It is possible that many deaths were attributed to other causes even though those deaths may have been precipitated or hastened by the sequelae of HIV/AIDS. This limitation is described in greater detail in Chapter 5. Furthermore, although the estimates of HIV and AIDS incidence were based on outputs from mathematical models which may more closely reflect the reality of HIV/AIDS incidence in Ontario, there is still some uncertainty regarding the parameters used in the model and whether the methods used to address missing exposure category information and selection bias associated with HIV testing patterns among individuals at varying risks to HIV infection were completely accurate. We also did not include the burden related to HIV-related malignancies or complications related to long-term antiretroviral therapy (e.g., cardiovascular disease).

4.3.3. *CHLAMYDIA TRACHOMATIS*

Chlamydia trachomatis (chlamydia) is an obligate intracellular pathogen that causes chlamydia, lymphogranuloma venereum and trachoma. The most common symptoms are painful sexual intercourse, pain/burning during urination, genital discharge and fever, although many people will be asymptomatic. Chlamydial infections can cause pelvic inflammatory disease, which can lead to infertility, chronic pelvic pain and ectopic pregnancies in women. Men can have urethritis (urethral inflammation), epididymitis (inflammation in the testicles) and prostatitis (prostate inflammation). Potential complications of chlamydia infection in neonates are conjunctivitis (ophthalmia neonatorum) and neonatal pneumonia. *C. trachomatis* also causes trachoma, a disease that leads to blindness.

Data sources and HALY calculation

Although chlamydia is a reportable disease in Ontario, reported cases were assumed to be a gross underestimate of true disease incidence because the disease is often not confirmed with laboratory testing (especially when treating sexual contacts and recurrent infections). On the other hand, many women are screened for chlamydia and may test positive in the absence of symptoms. Therefore, we used a syndrome-based approach to calculate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes chlamydia most commonly causes and the number of deaths due to chlamydial infection. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from chlamydial infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to chlamydia (to estimate both deaths and incident cases) and the duration of each health state. Additionally, we extracted the reported cases of chlamydia in infants (younger than one year) from Ontario's reportable disease database (iPHIS) to determine the number of cases of ophthalmia neonatorum and neonatal pneumonia contracted by newborns from an infected mother during delivery.

Exhibit 4.23

Parameters for estimating the disease burden due to *chlamydia trachomatis* (chlamydia)

Health State	Percentage of Syndrome Attributable to Chlamydia	Duration	Severity Weight	Episode Length	Number of Episodes	Number of Deaths
Pelvic inflammatory disease (females only)	21[100]	1 week[4]	0.086	60 days	2,950	1
Sequelae of PID						
Ectopic pregnancy	9 (% of PID cases among females of reproductive age)[101]	1 month[4]	0.448	N/A	203	0
Infertility	11 (% of PID cases among females of reproductive age)[101]	Until menopause[4]	0.107	N/A	247	0
Urethritis (males only)	30[102]	10 days[4]	0.039	30 days	2,504	0
Orchitis/Epididymitis (males only)	57[103]	2 weeks[4]	0.039	30 days	10,688	0
Cervicitis (females only)	16[104]	10 days[4]	0.039	30 days	45,167	0
Ophthalmia neonatorum (age 0–1 year)	15 (% of reported cases of chlamydia in this age group expected to develop this health state)[105]	2 weeks[4]	0.147	N/A	1	0
Neonatal pneumonia (age 0–1 year)	16 (% of reported cases of chlamydia in this age group expected to develop this health state)[105]	6 months[4]	0.136	N/A	1	0

Estimated burden

We estimated annual averages of one death and 61,761 health care utilization episodes attributable to chlamydia. The burden of chlamydia was significantly higher in females, and most of the burden affected those aged 15–44.

Limitations

These estimates for the burden of chlamydia are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. The quality of the reportable disease data is another potential limitation.

4.3.4. *NEISSERIA GONORRHEA*

Neisseria gonorrhea (gonorrhea) is a gram-negative bacterium that is responsible for the sexually transmitted infection known as gonorrhea. The most common symptoms are foul-smelling genital discharge, burning/painful urination and genital swelling. Although asymptomatic, infection is not uncommon. Gonorrhea is responsible for a host of other diseases, such as pelvic inflammatory disease, urethritis (urethral inflammation), prostatitis (prostate inflammation), orchitis (testicular inflammation) and conjunctivitis in newborns (ophthalmia neonatorum). Complications from gonorrhea can include infertility and ectopic pregnancies. Gonorrhea infections can be treated with antibiotics, and newborns commonly receive prophylactic treatment to prevent conjunctivitis.

Data sources and HALY calculation

Although gonorrhea is a reportable disease in Ontario, reported cases are likely a gross underestimate of true disease incidence because the disease is often not confirmed with laboratory testing (especially when treating sexual contacts and recurrent infections). On the other hand, many women are screened for gonorrhea and may test positive in the absence of symptoms. Therefore, we used a syndrome-based approach to calculate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes gonorrhea most commonly causes and the number of deaths due to gonococcal infection. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from gonococcal infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to gonorrhea (to estimate both deaths and incident cases) and the duration of each health state. Additionally, we extracted the reported cases of gonorrhea in infants (younger than one year) from Ontario's reportable disease database (iPHIS) to determine the number of cases of ophthalmia neonatorum.

Exhibit 4.24

Parameters for estimating the disease burden due to *Neisseria gonorrhea* (gonorrhea)

Health State	Percentage of Health State Attributable to Gonorrhea	Duration	Severity Weight	Episode Length	Number of Episodes	Number of Deaths
Pelvic inflammatory disease (females only)	19[100]	1 week[4]	0.086	60 days	2,670	1
Sequelae of PID						
Ectopic pregnancy	9 (% of PID cases among females of reproductive age)[101]	1 month[4]	0.448	N/A	183	0
Infertility	11 (% of PID cases among females of reproductive age)[101]	Until menopause[4]	0.107	N/A	224	0
Urethritis (males only)	70[102]	10 days[4]	0.039	30 days	5,843	0
Orchitis/Epididymitis (males only)	34[103]	2 weeks[4]	0.039	30 days	6,375	0
Cervicitis (females only)	6[104]	10 days[4]	0.039	30 days	16,938	0
Ophthalmia neonatorum (0–1 year age group)	81 (% of reported cases of gonorrhea in this age group expected to develop this health state)[106]	2 weeks[4]	0.147	N/A	1	0

Estimated burden

We estimated annual averages of one death and 32,234 health care utilization episodes attributable to gonorrhea. The burden of gonorrhea was significantly higher in females, and most of the burden affected those aged 15–44.

Limitations

These estimates for the burden of gonorrhea are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. The quality of the reportable disease data is another potential limitation.

4.3.5. HERPES SIMPLEX VIRUS

Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) are transmitted by close contact of mucosal surfaces (oral or genital), as well as vertical transmission during delivery. HSV-1 generally causes oral herpes (cold sores), and HSV-2 more frequently causes genital herpes (painful, genital ulcers). After initial infection, HSV remains dormant for life within the nerves and periodically activates to cause recurrent infection. More rarely, it can cause life-threatening infections such as encephalitis (inflammation of the brain). Antiviral medications can decrease the risk of spreading the disease, but there is no cure to eradicate infection.

Data sources and HALY calculation

HSV is not a reportable disease in Ontario (except in neonates) and is often asymptomatic. Most of the burden is expected in the ambulatory setting, but there is no specific diagnostic code for HSV in physician billing claims. For this reason, an agent-based approach was used where incidence estimates were derived from epidemiologic studies. For YLL, we used Ontario vital statistics data to determine the number of deaths due to anogenital herpes viral infection (herpes simplex) and herpes viral infection. For YERF, we derived age- and sex-specific incidence rates of symptomatic HSV-2 from a seroprevalence study of HSV-2 conducted by Howard et al. in Ontario.[107] Additionally, we extracted the reported cases of neonatal herpes (birth to one year, which was the finest age stratum possible) from Ontario's reportable disease database (iPHIS) to account for the burden of herpes due to vertical transmission, with 40% of these reported cases expected to develop long-term sequelae.[108] We used health care utilization data to determine the number of episodes of encephalitis in Ontario and attributed 20% of these episodes to the herpes virus.[109]

Exhibit 4.25

Parameters for estimating the disease burden due to herpes simplex virus (HSV)

Health State	Percentage of Modeled Symptomatic HSV Cases that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Primary genital herpes syndrome	50[108]	10.5 days[108]	0.068	7,337
First symptomatic episode without primary genital herpes syndrome	50[108]	4 days [108]	0.023	7,337
Recurrent herpes	100[103]	87 days (males) 66 days (females)[108]	0.023	14,675
Encephalitis	N/A (used 20% of encephalitis cases from health administrative data)[109]	3 weeks[27]	0.502	224
Neonatal herpes with long-term sequelae	N/A (assumed 40% developed long-term sequelae)[108]	Half of life expectancy from birth	0.652	2

Estimated burden

We estimated annual averages of seven deaths and 14,677 incident cases attributable to HSV, as well as 224 health care utilization episodes of encephalitis. Disease burden attributed to HSV was relatively similar between males and females. Most of the disease burden was in individuals aged 14–44; however, there was also substantial disease burden in neonates. All seven deaths from herpes were due to encephalitis.

Limitations

These estimates for the burden of HSV are subject to the limitations of the various data sources employed. For genital herpes, there is uncertainty related to estimating incidence by applying mathematical modeling techniques to prevalence estimates. Unfortunately, there is no specific code for genital herpes in the physician billing claims dataset. The estimate for encephalitis is limited by uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. The estimate for neonatal herpes relies on the quality of the reportable disease data. Lastly, we likely underestimated the YERF of HSV by not including mucocutaneous herpes (i.e., cold sores).

4.3.6. *TREPONEMA PALLIDUM*

Treponema pallidum (syphilis) is a bacterium that causes the disease known as syphilis; it is spread primarily by sexual contact. After a variable incubation of days to months, "primary syphilis" can develop, which involves a painless genital ulcer that heals spontaneously. However, several weeks later many patients progress to "secondary syphilis," which most commonly causes a widespread rash but can also cause inflammation of virtually any organ system. Years to decades later, some patients develop "tertiary syphilis". This may result in cardiac complications or, more commonly, in "neurosyphilis", which can involve degenerative brain disease and spinal cord problems. Mother-to-child transmission can also occur resulting in a congenital syndrome characterized by rash, abnormalities of skull and bone development, liver enlargement and blood cell abnormalities. Syphilis can be treated by antibiotics, and most complications can be prevented if treated in time.

Data sources and HALY calculation

In this study, we generally used an agent-based approach to quantify disease burden where reported disease data were available. However, most epidemiologic studies describing the clinical course of syphilis were several decades old and focused on untreated syphilis, which we assumed would be rare in Ontario. Therefore, we did not use these published transition parameters to estimate cases that would progress to future health states and instead used reportable disease data to directly calculate the disease burden of each health state in the present. For YLL, Ontario vital statistics data were used to determine the number of deaths due to syphilis. For YERF, we determined reported cases of primary, secondary, neurological, and congenital syphilis from Ontario reported disease data (iPHIS). We assumed that all reported cases of secondary syphilis had also recently experienced the primary syphilis health state but were not diagnosed during the primary episode. Therefore, the number of primary syphilis cases was the sum of the reported number of primary and secondary syphilis cases. There were approximately 80 annual cases of "syphilis, unspecified" in the reportable disease dataset. We classified these as primary syphilis because that would lead to the most conservative estimate and would proportionately be the most likely state they would represent. We used epidemiologic studies to determine the duration of primary, secondary, neurological and congenital syphilis.

Exhibit 4.26
Parameters for estimating the disease burden due to *Treponema pallidum* (syphilis)

Health State	Disease Duration	Severity Weight	Number of Cases Expected to Develop Health State
Primary syphilis	14 days[4]	0.017	344*
Secondary syphilis	28 days[4]	0.039	149
Neurosyphilis	10 years[4]	0.074	22
Congenital syphilis	3 years[4]	0.139	1

* Includes 80 cases per year of "syphilis, unspecified."

Estimated burden
We estimated annual averages of 0 deaths and 367 incident cases of syphilis. The entire disease burden was from YERF, with 94% of the burden due to neurosyphilis. The burden was higher in males and in individuals aged 30–64.

Limitations
A major limitation of these estimates of syphilis disease burden is the high likelihood of underdiagnosis and underreporting. The burden of tertiary syphilis is likely from remote and/or imported infection and therefore may not represent the burden expected with a true "incidence-based approach" (i.e., expected cases of tertiary syphilis in the future arising from current incidence of syphilis infections). The expected burden may be lower due to improved diagnostic and treatment practices but may be higher if many current cases are undiagnosed or if there are many imported cases in the future. Classifying all "syphilis, unspecified" cases as primary syphilis may underestimate the burden of syphilis. On the other hand, assuming that all cases initially reported as secondary syphilis had symptomatic primary syphilis may overestimate the burden, because the primary episode in these individuals may have been less severe than for individuals whose primary episodes were diagnosed and reported. Finally, the validity of these estimates is dependent on the quality of the reportable disease data. The limitations of these data are described in greater detail in Chapter 5.

4.4 VIRAL RESPIRATORY INFECTIONS

Infectious agents assigned to this disease group all cause a similar constellation of syndromes (upper respiratory tract infection, acute bronchitis, bronchiolitis, pneumonia and otitis media). Excluding influenza, these infectious agents are not reportable diseases.

Within this disease group, influenza was calculated to have the highest disease burden, with rhinovirus and respiratory syncytial virus (RSV) ranking second and third, respectively (Exhibit 4.27). More than half of the disease burden (53%) was from premature mortality. However, disease burden due to reduced functioning (47%) was more prominent in this disease grouping compared to other groupings (e.g., compared to 11% of the burden from common bacterial infections). The disease burden was generally higher in females, particularly for influenza (Exhibit 4.28).

Exhibit 4.27

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for viral respiratory infections

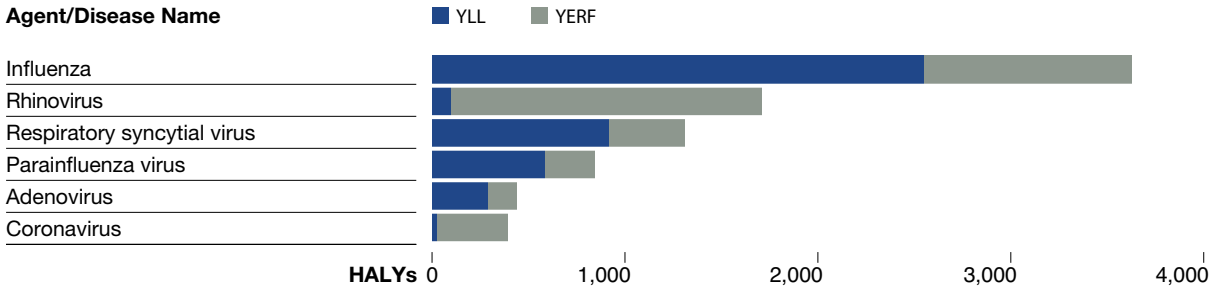
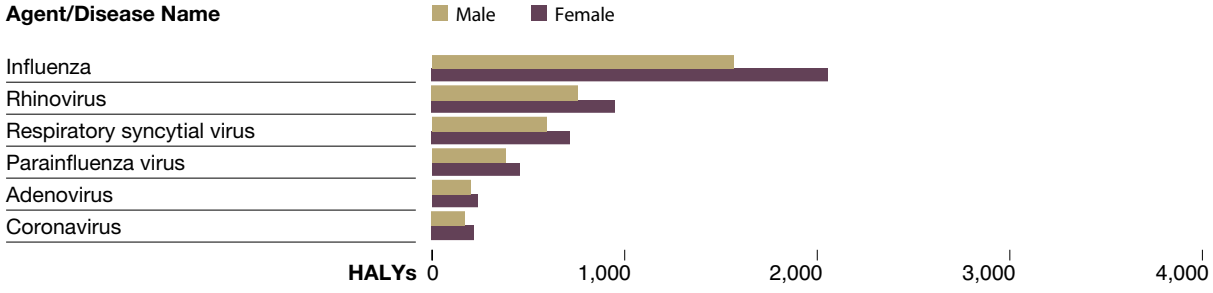


Exhibit 4.28

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for viral respiratory infections, by sex



4.4.1. INFLUENZA

Influenza is a virus transmitted by respiratory droplets and possibly by airborne spread; it is responsible for seasonal epidemics during the winter months in temperate climates. After a brief incubation period of one to two days, patients typically develop fever, muscle pain, cough and sore throat. In some patients, influenza can progress to produce influenza pneumonia, or can be complicated by secondary bacterial pneumonia. Other complications range from mild otitis media (middle ear infection) to bronchitis and bronchiolitis. Although vaccines are available for influenza, the rapid evolution of these viruses relating to changes in the surface proteins mean that a new vaccine needs to developed prior to each influenza season. Occasionally, a major genetic reassortment between influenza viruses occurs (involving human, bird and/or swine strains) resulting in a new virus to which the majority of the human population is susceptible. The result is an influenza pandemic, with the potential for very large numbers of cases and deaths.

Data sources and HALY calculation

Although influenza is a reportable disease in Ontario, the vast majority of individuals who seek medical attention for an influenza infection do not have samples collected for laboratory testing and confirmation. Therefore, using reported cases of influenza would severely underestimate its burden in Ontario. For this reason, we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes influenza most commonly causes. Additionally, the vital statistics data were used to capture the number of deaths coded as influenza. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from influenza infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to influenza (to estimate both deaths and incident cases) and the duration of each health state.

...the vast majority of individuals who seek medical attention for an influenza infection do not have samples collected for laboratory testing and confirmation.

Exhibit 4.29
Parameters for estimating the disease burden due to influenza

Syndrome (health state)	Percentage of Syndrome Attributable to Influenza	Duration	Severity Weight	Episode Length (days)	Number of Episodes	Number of Deaths[a]
Pneumonia	10[110]	2 weeks[27]	0.136	30	25,247	195
Acute bronchitis	24[42]	2 weeks[43]	0.086	30	238,201	3
Bronchiolitis	6[111]	2 weeks[112]	0.057	30	526	0
Otitis media	5[113]	4.5 days[45]	0.052	30	37,388	0
Upper respiratory infection	10[114]	1 week	0.023	15	319,789	0

[a] Excludes the 74 deaths per year coded as "influenza" in the vital statistics data

Estimated burden

We estimated annual averages of 272 deaths and 621,151 health care utilization episodes attributable to influenza. There was a higher burden of influenza in females compared to males. This can most likely be attributed to influenza and pneumonia deaths being more common in the older age groups which have higher numbers of women than men, and perhaps due to sex-specific differences in health-seeking behaviour. In terms of premature mortality, most of the burden was in individuals aged 65 or older, mainly due to a large number of pneumonia and influenza deaths in this age group. In terms of YERF, the burden was relatively equal across age groups as acute bronchitis and upper respiratory tract infections comprise the majority of incident cases and they are distributed relatively evenly throughout age groups.

Limitations

These estimates for the burden of influenza are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. These limitations are particularly problematic for influenza because the vast majority of influenza cases are not subjected to diagnostic testing, and even among tested cases the sensitivity of detection is quite low. In addition, much of influenza's burden occurs indirectly by aggravation of other comorbidities, such as coronary artery disease, chronic obstructive pulmonary disease and congestive heart failure. Our approach does not capture events that may be attributable to influenza but are coded as conditions other than those included in the above table (e.g., increases in cardiovascular morbidity and mortality that are associated with influenza activity). Schanzer and colleagues have estimated that nearly 4,000 deaths per year in Canada are attributed to influenza.[115] This translates to roughly 1,600 deaths in Ontario. Therefore, our estimate of 272 deaths annually is likely an underestimate of the true burden of influenza. A limitation of our estimate of YERF is that we did not adjust for symptomatic cases that did not seek medical care.

4.4.2. RHINOVIRUS

Rhinoviruses refer to a group of viruses that are the main cause of the common cold. They are the most common viral infections in humans. They are spread through droplet transmission, contaminated objects and person-to-person contact. Common symptoms exhibited include runny nose, congestion, cough and sore throat. Patients will frequently experience fatigue, malaise (feeling unwell), myalgias (muscle aches), fever and anorexia (loss of appetite). There is no treatment available for the common cold, and prevention revolves around hand hygiene.

Data sources and HALY calculation

Rhinovirus is not a reportable disease, therefore we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes rhinovirus most commonly causes. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from rhinovirus infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to rhinovirus (to estimate both deaths and incident cases) and the duration of each health state.

Exhibit 4.30
Parameters for estimating the disease burden due to rhinovirus

Syndrome (health state)	Percentage of Syndrome Attributable to Rhinovirus	Duration	Severity Weight	Episode Length (days)	Number of Episodes	Number of Deaths
Acute bronchitis	33[42]	2 weeks[43]	0.086	30	327,526	4
Bronchiolitis	16[111]	2 weeks[112]	0.057	30	1,403	0
Otitis media	1[116]	4.5 days[45]	0.052	30	7,478	0
Upper respiratory infection	40[114]	1 week	0.023	15	1,279,154	1

Estimated burden

We estimated annual averages of five deaths and 1,615,561 health care utilization episodes attributable to rhinovirus. The burden of rhinovirus was relatively equal between males and females. Most of the disease burden was from YERF. Disease burden was relatively equal across age groups, as acute bronchitis and upper respiratory tract infections comprise the majority of incident cases, and they are distributed fairly evenly throughout the age groups. However, disease burden diminished over 60 years of age.

Limitations

These estimates for the burden of rhinovirus are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. A further limitation is that we did not adjust for symptomatic cases that did not seek medical care, so the estimated burden may be an underestimate. Lastly, rhinovirus causes milder disease than other respiratory viruses, so the validity of the assumption of a constant severity weight for all pathogens causing a particular syndrome is uncertain.

4.4.3. RESPIRATORY SYNCYTIAL VIRUS

Respiratory syncytial virus (RSV) is responsible for numerous respiratory infections in the infant population. It is transmitted through droplets in the air, contaminated objects or via person-to-person contact. Outbreaks occur from fall to spring and peak during the winter. For most patients, an RSV infection mimics the common cold with stuffy/runny nose, cough, low-grade fever and sore throats being common symptoms. However, complications can include bronchiolitis (inflammation of the airways requiring hospitalization) and pneumonia. Treatment of RSV infections is focused on supportive management. Passive vaccination using immunoglobulins is offered to infants at high risk of complications, such as premature babies.

Data sources and HALY calculation

RSV is not a reportable disease, therefore we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes RSV most commonly causes. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from RSV infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to RSV (to estimate both deaths and incident cases) and the duration of each health state.

Exhibit 4.31
Parameters for estimating the disease burden due to respiratory syncytial virus (RSV)

Syndrome (health state)	Percentage of Syndrome Attributable to RSV	Duration	Severity Weight	Episode Length (days)	Number of Episodes	Number of Deaths
Pneumonia	21 (0–14 years)[117] 2 (15–64 years)[110] 5 (≥65 years)[118]	2 weeks[27]	0.136	30	18,687	95
Acute bronchitis	2.5 (0–64 years)[42] 12 (≥65 years)[119]	2 weeks[43]	0.086	30	45,112	1
Bronchiolitis	64[111]	2 weeks[112]	0.057	30	5,613	0
Otitis media	15[113]	4.5 days[45]	0.052	30	112,165	0
Upper respiratory infection	5[114]	1 week	0.023	15	159,894	0

Estimated burden

We estimated annual averages of 96 deaths and 341,471 health care utilization episodes attributable to RSV. The burden of RSV was relatively equal between males and females. Most of the disease burden was in children aged from birth to 14 years (with 13% of the burden in children aged from birth to four years) and the elderly aged 65 and older. The high burden in children under the age of 14 years can be attributed to the large proportion of pneumonia (21%) due to RSV in children. The burden of RSV in individuals aged 65 or older was a result of pneumonia deaths in this age group.

Limitations

These estimates for the burden of RSV are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. A further limitation is that we did not adjust for symptomatic cases that did not seek medical care, and so we may have underestimated population morbidity. Alternative methods of estimation which make use of the seasonality of the virus might be worth exploring in future analyses.

4.4.4. PARAINFLUENZA

Parainfluenza is a group of viruses that are responsible for both upper and lower respiratory tract infections in young children. The viruses are spread through droplets in the air, contaminated objects and via person-to-person transmission. Parainfluenza viruses cause the majority of cases of croup, an illness presenting with a bark-like cough, inspiratory stridor (high-pitched sound during inhalation), fever and hoarseness. Severe cases require hospital admission for monitoring and treatment. Complications of parainfluenza infection include acute bronchitis and pneumonia (lung infection). Patients are treated with supportive measures such as oxygen in addition to epinephrine and steroids. The seasonality of parainfluenza is often distinct from other respiratory viruses. There are no vaccines available for parainfluenza infections.

Data sources and HALY calculation

Parainfluenza is not a reportable disease, therefore, we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes parainfluenza most commonly causes. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from parainfluenza infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to parainfluenza (to estimate both deaths and incident cases) and the duration of each health state.

Exhibit 4.32
Parameters for estimating the disease burden due to parainfluenza

Syndrome (health state)	Percentage of Syndrome Attributable to Parainfluenza	Duration	Severity Weight	Episode Length (days)	Number of Episodes	Number of Deaths
Pneumonia	3[112]	2 weeks[27]	0.136	30	7,574	59
Acute bronchitis	3.8[42]	2 weeks[43]	0.086	30	37,219	0
Otitis media	6.5[113]	4.5 days[45]	0.052	30	48,605	0
Upper respiratory infection	5[114]	1 week	0.023	15	159,894	0

Estimated burden

We estimated annual averages of 59 deaths and 253,292 health care utilization episodes attributable to parainfluenza. The disease burden of parainfluenza was relatively similar between females and males. There was a greater burden in the older age groups, likely due to pneumonia deaths in the elderly caused by parainfluenza.

Limitations

These estimates for the burden of parainfluenza are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. A further limitation is that we did not adjust for symptomatic cases that did not seek medical care, so the estimated burden may be an underestimate. Alternative methods of estimation which make use of the different seasonality of the virus might be worth exploring in future analyses.

4.4.5. ADENOVIRUS

Adenoviruses are involved in numerous infections after being transmitted via droplets, contaminated objects and fecal-oral routes. Infections from adenoviruses can manifest as tonsillitis (inflammation of the tonsils), conjunctivitis (eye infection), otitis media (ear infection), bronchiolitis (infection of the airways) and pneumonia. Treatment is supportive, and uncomplicated adenovirus infections resolve spontaneously. There are no vaccines available for adenovirus infections.

Data sources and HALY calculation

Adenovirus is not a reportable disease; therefore, we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes adenovirus most commonly causes. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from adenovirus infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to adenovirus (to estimate both deaths and incident cases) and the duration of each health state.

Exhibit 4.33
Parameters for estimating the disease burden due to adenovirus

Syndrome (health state)	Percentage of Syndrome Attributable to Adenovirus	Duration	Severity Weight	Episode Length (days)	Number of Episodes	Number of Deaths
Pneumonia	1.5[110]	2 weeks[27]	0.136	30	3,787	29
Bronchiolitis	7.5[120]	2 weeks[107]	0.057	30	658	0
Otitis media	5[113]	4.5 days[45]	0.052	30	37,388	0
Upper respiratory infection	2.5[114]	1 week	0.023	15	79,947	0
Conjunctivitis	20[46]	2 weeks[121]	0.023	15	81,613	0

Estimated burden

We estimated annual averages of 29 deaths and 203,393 health care utilization episodes attributable to adenovirus. The burden of adenovirus was relatively equal between males and females. The disease burden was distributed relatively evenly across age groups but was weighted more heavily in those older than 65 because most of the small number of pneumonia deaths due to adenovirus occurred in older individuals.

Limitations

These estimates for the burden of adenovirus are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. A further limitation is that we did not adjust for symptomatic cases that did not seek medical care, so the estimated burden may be an underestimate. Lastly, adenovirus may cause milder disease than other respiratory viruses, so the validity of the assumption of a constant severity weight for all pathogens causing a particular syndrome is uncertain.

4.4.6. CORONAVIRUS

Coronaviruses are a group of viruses that are most infamous in Ontario as the causative agent of Severe Acute Respiratory Syndrome (SARS), but the usual strains are much less virulent and are an important cause of the common cold. They are spread through droplet transmission, contaminated objects and person-to-person contact. SARS has not circulated since the outbreak in 2003.

Data sources and HALY calculation

Coronavirus is not a reportable disease; therefore, we used a syndrome-based approach to estimate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to each of the syndromes coronavirus most commonly causes; although vital statistics data from 2003 were included in this analysis, deaths due to SARS were not included, even though the causative agent was a coronavirus. For YERF, we used Ontario health care utilization data to determine the number of episodes of each of the syndromes resulting from coronavirus infection. We used epidemiologic studies to determine the percentage of each syndrome attributable to coronavirus (to estimate both deaths and incident cases) and the duration of each health state.

Exhibit 4.34
Parameters for estimating the disease burden due to coronavirus

Syndrome (health state)	Percentage of Syndrome Attributable to Coronavirus	Duration (weeks)	Severity Weight	Episode Length (days)	Number of Episodes	Number of Deaths
Acute bronchitis	6.3[42]	2[43]	0.086	30	62,031	1
Upper respiratory infection	12.5[114]	1	0.023	15	399,736	0

Estimated burden

We estimated annual averages of one death and 461,767 health care utilization episodes attributable to coronavirus. The burden of coronavirus was relatively equal between females and males. The disease burden was similar across age groups, as acute bronchitis and upper respiratory tract infections were evenly distributed throughout age groups. However, disease burden was slightly lower over age 60.

Limitations

These estimates for the burden of coronavirus are limited by the numerous sources of uncertainty arising from the assignment of non-specific events in Ontario vital statistics and health care utilization data using attributable fractions from various epidemiologic studies. A further limitation is that we did not adjust for symptomatic cases that did not seek medical care, so the estimated burden may be an understated. Coronavirus may cause milder disease than other respiratory viruses, therefore the validity of the assumption of a constant severity weight for all pathogens causing a particular syndrome is uncertain. There is no ICD code for SARS coronavirus, so although we included mortality data from 2003 (when there were known deaths from SARS in Ontario),[122] we could not capture those deaths using our methodology.

4.5 INTESTINAL INFECTIONS

Infectious agents assigned to this disease group are some of the most common gastrointestinal infections (although two notable omissions are norovirus and rotavirus, both very common causes of viral gastroenteritis). With the exception of *Clostridium difficile*, all of these intestinal infections are reportable diseases.* However, not all individuals infected with one of these gastrointestinal agents will seek medical care for their symptoms. For this reason, we adjusted for underreporting of cases of intestinal infection where possible.

Within this disease group, *C. difficile* was calculated to have by far the highest disease burden (Exhibit 4.35). *C. difficile* had a much higher burden because it caused much more premature mortality than the other agents. For most intestinal infections, disease burden was relatively similar between males and females (Exhibit 4.36). However, there were some exceptions as the burden of *C. difficile* was much higher in females compared to males, and the burden of *Shigella* and *Listeria* was much higher in males than females.

Exhibit 4.35
Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for intestinal infections

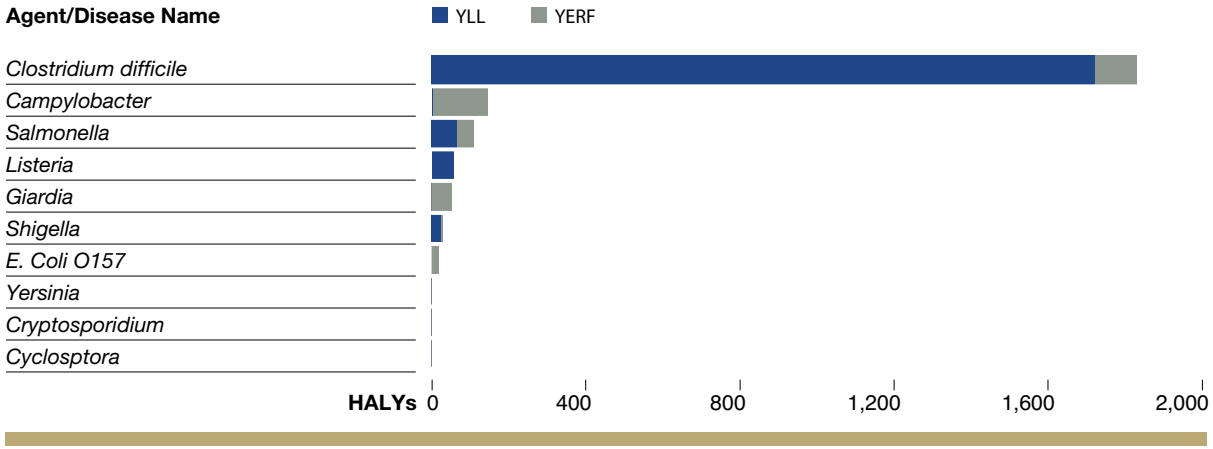
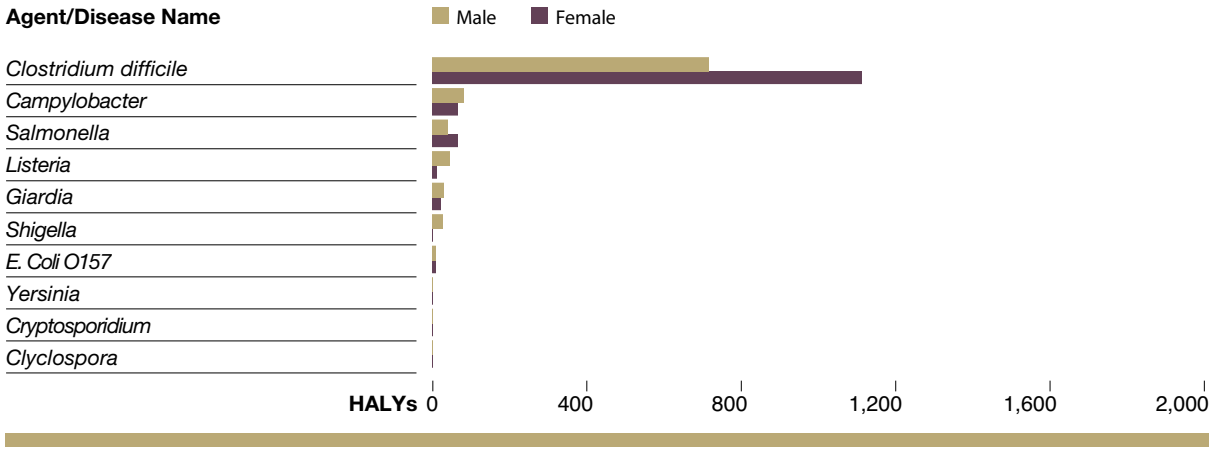


Exhibit 4.36
Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for intestinal infections, by sex



* Reporting of aggregate counts of C. difficile was mandated by the Ontario Ministry of Health and Long-Term Care in August 2008.

4.5.1. *CLOSTRIDIUM DIFFICILE*

Clostridium difficile (*C. difficile*) is an anaerobic bacterium that can produce colitis (intestinal infection) in patients whose normal protective bowel flora has been disrupted (usually due to recent antibiotic use). The organism releases toxins which lead to profuse watery diarrhea, and have the potential to cause bowel distension, perforation, systemic inflammatory response and death. A minority of patients require colectomy (bowel removal) to achieve cure, and the attributable mortality rate of this predominantly hospital-acquired infection is 5%.[123]

Data sources and HALY calculation

Unlike most intestinal infections, *C. difficile* was not a reportable disease in Ontario during the study period, therefore we used health care utilization data to determine the number of episodes of enterocolitis due to *C. difficile*. Once enterocolitis cases attributable to *C. difficile* were extracted, we used an agent-based approach to determine disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths from enterocolitis due to *C. difficile*. For YERF, we used Ontario health care utilization data to determine the number of episodes of enterocolitis caused by *C. difficile*. We used epidemiologic studies to determine the percentage of *C. difficile* enterocolitis cases that progressed to a post-colectomy state and the duration of illness for each health state.

Exhibit 4.37
Parameters for estimating the disease burden due to *Clostridium difficile* (*C. difficile*)

Health State	Percentage of *C. Difficile* Cases that Progress to Each Health State	Duration	Severity Weight	Episode Length	Number of Cases Expected to Develop Health State
Enterocolitis	100	2 weeks[124]	0.123	**60 days**	5,364
Post-colectomy state	1[125]	Lifetime	0.041	**N/A**	54

Estimated burden

We estimated annual averages of 167 deaths and 5,364 incident cases attributable to *C. difficile*. Most of the burden assigned to *C. difficile* was due to premature mortality. The burden was much higher in females than males. This may be partially explained by the fact that there are a higher percentage of women in the older age groups and *C. difficile* risk increases with age. Most of the burden for *C. difficile* was among individuals aged 65 and older.

Limitations

These estimates for the burden of *C. difficile* likely underestimate the true burden because they only include cases that were severe enough to require hospitalization or a visit to an emergency department. Because there is no diagnostic code in the physician billing claims data for *C. difficile*, we could not account for individuals with less severe infections presenting only to their family physician. Furthermore, we were unable account for those who did not seek medical care at all. The proportion of deaths attributed to *C. difficile* is likely underreported due to the presence of comorbid conditions which are more likely to be coded as the cause of death. We also could not distinguish between infections acquired in health care versus community settings. Additional burdens not considered in this study include hospital closures due to outbreaks of *C. difficile*, which in turn can lead to economic repercussions, interference with health care delivery, undermining of public confidence and litigation.

4.5.2. *CAMPYLOBACTER*

Campylobacter are spiral, gram-negative bacteria that are spread by contaminated food and water, eating raw meat, drinking raw milk and, rarely, by sexual contact. They infect the intestine and cause gastroenteritis (inflammation of the gastrointestinal tract) with symptoms, including bloody diarrhea, cramps, fever and pain. Occasionally, people can experience immune-mediated complications such as reactive arthritis or Guillain-Barré Syndrome ([GBS] ascending nerve paralysis). Antibiotics can be used to shorten the course of the disease.

Data sources and HALY calculation

Since *Campylobacter* enteritis is a reportable disease in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to *Campylobacter* enteritis. For YERF, we extracted reported cases of Campylobacter enteritis from Ontario's reportable disease database (iPHIS). Since reported cases underestimate the actual number cases, we used a Canadian study by Thomas et al. that collated data from multiple sources to quantify the underreporting of *Campylobacter*.[126] Using the conservative estimate from this paper, there were 23 *Campylobacter* cases in the community for every reported case. We used epidemiologic studies to determine the percentage of *Campylobacter* cases that progressed to the following health states: gastroenteritis – mild (did not seek medical care), gastroenteritis – moderate (saw a physician), gastroenteritis – severe (hospitalized), reactive arthritis, GBS and inflammatory bowel disease. The same denominator (i.e., number of estimated cases adjusted for underreporting) was used for all health states, but we assumed that individuals who had severe gastroenteritis, reactive arthritis, GBS or inflammatory bowel disease had a prior episode of moderate gastroenteritis (i.e., saw a physician). Epidemiologic studies were also used to determine the durations of the health states.

Exhibit 4.38
Parameters for estimating the disease burden due to *Campylobacter*

Health State	Percentage of *Campylobacter* Cases in the Community that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Gastroenteritis – mild	76[38]	3.5 days[38]	0.023	67,550
Gastroenteritis – moderate	24[38]	9.7 days[38]	0.041	21,016
Gastroenteritis – severe	1[38]	14.5 days[38]	0.086	856
Reactive arthritis	1.7[38]	222 days[38]	0.041	1501
Guillain-Barré Syndrome	0.1[38]	6 months[127]	0.132	89
Inflammatory bowel disease	0.04[38]	Lifetime[38]	0.039	33

Estimated burden

We estimated annual averages of 0.33 deaths and 88,566 incident cases (3,387 before adjustment for underreporting) attributable to *Campylobacter* enteritis. Most of the disease burden was due to reduced functioning. Disease burden was similar between males and females, and most of the burden was in individuals aged 20–64.

Limitations

Although we were able to adjust for underdiagnosis and underreporting of *Campylobacter* based on a Canadian study, the validity of these estimates is dependent on the quality of the reportable disease data. Suspected underreporting of *Campylobacter* deaths in the vital statistics data is another major limitation.

4.5.3. *SALMONELLA*

Salmonella species are transmitted by contaminated foods such as eggs, cheese, meats and vegetables, as well as by person-to-person transmission through the fecal-oral route. Salmonellosis results in gastroenteritis (inflammation of the gastrointestinal tract) with diarrhea, fever, vomiting and abdominal pain. Severe dehydration requiring hospitalization occasionally occurs. Septicaemia (bloodstream infection) occurs in 5% of patients, and infection can more rarely occur in other body sites causing endocarditis (heart valve infection) and osteoarthritis (bone infection). Antibiotics can decrease the severity and length of the disease but may prolong carriage. The burden described in this section is to be distinguished from the burden associated with *Salmonella typhi* and *Salmonella paratyphi*, the causes of typhoid fever and paratyphoid fever, which are considered separately under imported infections (section 4.9). Those two pathogens are usually transmitted by the fecal-oral route.

Data sources and HALY calculation

Since salmonellosis is a reportable disease in Ontario, we calculated disease burden by using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to *Salmonella*. For YERF, we extracted reported cases of salmonellosis from Ontario's reportable disease database (iPHIS). Since reported cases may underestimate the actual number of cases, we used a Canadian study by Thomas et al. that used data from multiple sources to quantify the underreporting of *Salmonella*.[126] Using the conservative estimate from this paper, there were 13 *Salmonella* cases in the community for every reported case. We used epidemiologic studies to determine the percentage of *Salmonella* cases that progressed to the following health states: gastroenteritis – mild (did not seek medical care), gastroenteritis – moderate (saw a physician), gastroenteritis – severe (hospitalized), and septicaemia. The same denominator (i.e., number of estimated cases adjusted for underreporting) was used for all health states, but we assumed that individuals who had severe gastroenteritis or septicaemia had a prior episode of moderate gastroenteritis (i.e., saw a physician). Epidemiologic studies were also used to determine the durations of the health states.

Exhibit 4.39
Parameters for estimating the disease burden due to *Salmonella*

Health State	Percentage of *Salmonella* Cases in the Community that Progress to each Health State	Duration (days)	Severity Weight	Number of Cases Expected to Develop Health State
Gastroenteritis – mild	85[38]	5.5[38]	0.023	29,732
Gastroenteritis – moderate	15[38]	10.5[38]	0.041	5,343
Gastroenteritis – severe	2[38]	16[38]	0.086	635
Septicaemia	5[128]	7[38]	0.652	1,735

Estimated burden

We estimated annual averages of two deaths and 34,693 incident cases (2,711 before adjustment for underreporting) attributable to *Salmonella*. Disease burden was slightly higher in females. Most of the burden was in individuals aged 20–64.

Limitations

Although we were able to adjust for underdiagnosis and underreporting of *Salmonella* based on a Canadian study, the validity of these estimates is dependent on the quality of the reportable disease data. The limitations of these data are described in greater detail in Chapter 5. Due to the rarity of the outcomes, burden secondary to endocarditis and osteoarthritis were not included. Suspected underreporting of *Salmonella* deaths in the vital statistics data is another limitation.

4.5.4. *LISTERIA MONOCYTOGENES*

Listeria monocytogenes (*Listeria*) is a bacterium that causes a food-borne infection; it is found in unpasteurized dairy products and uncooked foods such as deli meats (because its growth is not prevented by refrigeration). After a one-day incubation, it can result in gastroenteritis (inflammation of the gastrointestinal tract) causing fever and diarrhea. Invasive infection can include septicaemia (bloodstream infection), meningitis (cerebrospinal fluid infection) and brain abscess among other sites. These invasive infections are more common in pregnant women, people over 50 years, and those with deficiencies in their immune system. Antibiotic treatment is used as the mainstay of therapy. Given recent outbreaks in Canada, *Listeria* is routinely tested for at deli meat plants.

Data sources and HALY calculation

Since listeriosis is a reportable disease in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to *Listeria*. For YERF, we extracted reported cases of listeriosis from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute infectious episode of gastroenteritis. We used epidemiologic studies to determine the percentage of reported listeria cases that progressed to septicaemia and bacterial meningitis and to determine the duration of the health states.

Exhibit 4.40
Parameters for estimating the disease burden due to *Listeria monocytogenes* (*Listeria*)

Health State	Percentage of Reported Listeriosis Cases that Progress to Each Health State	Duration (weeks)	Severity Weight	Number of Cases Expected to Develop Health State
Gastroenteritis	100	1[38]	0.041	39
Septicaemia	21[129]	1[38]	0.652	8
Bacterial meningitis	40[129]	2[35]	0.652	16

Estimated burden

We estimated annual averages of two deaths and 39 incident cases attributable to *Listeria*. Disease burden was higher in males and among younger age groups.

Limitations

These estimates for the burden of *Listeria* are dependent on the quality of the reportable disease data; the limitations of these data are described in greater detail in Chapter 5. There is a high likelihood of underdiagnosis and underreporting, that we were unable to adjust for because we could not find any epidemiologic studies with empirical data. However, because most of the disease burden due to *Listeria* was from YLL rather than YERF, adjustment for underreporting (which would have changed only the YERF estimate) likely would not have significantly changed the estimate of disease burden. Our methodology could not account for year-to-year fluctuations in listeriosis as exemplified by the province-wide outbreak in 2008, which occurred after our study period. We also did not include adverse pregnancy outcomes due to their relative rarity. Finally, we did not consider the economic impact of outbreaks related to *Listeria*.

4.5.5. *GIARDIA LAMBLIA*

Giardia lamblia (*Giardia*) is a protozoan parasite which causes giardiasis and is spread through contaminated water systems, fresh water sources, food and the fecal-oral route. The symptoms of *Giardia* gastroenteritis (inflammation of the gastrointestinal tract) include explosive watery diarrhea, abdominal pains, vomiting and fever. These symptoms can become chronic, and complications such as dehydration, weight loss, anorexia and fatigue can ensue. Antibiotic treatment is commonly prescribed; however, there are an increasing number of treatment-refractory cases.

Data sources and HALY calculation

Since giardiasis is a reportable disease in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to *Giardia*. For YERF, we extracted reported cases of giardiasis from Ontario's reportable disease database (iPHIS) and treated each reported case as an infectious episode associated with acute diarrhea. We used epidemiologic studies to determine the percentage of reported *Giardia* cases that progressed to chronic giardiasis and to determine the duration of the health states.

Exhibit 4.41
Parameters for estimating the disease burden due to *Giardia lamblia* (*Giardia*)

Health State	Percentage of Reported Giardiasis Cases that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Infectious episode with acute diarrhea	100	2 weeks[130]	0.041	1,596
Chronic giardiasis	40[131]	1.9 years[143]	0.041	638

Estimated burden

We estimated annual averages of 0 deaths and 1,596 incident cases attributable to *Giardia*. Since there were no recorded *Giardia* deaths, the entire disease burden attributed to *Giardia* was from reduced functioning. Disease burden was relatively similar between males and females and peaked in those aged 30–45.

Limitations

These estimates for the burden of *Giardia* are dependent on the quality of the reportable disease data. There is a high likelihood of underdiagnosis and underreporting that we were unable to adjust for because we could not find any epidemiologic studies with empirical data. However, unlike *Listeria*, where most of the burden was due to premature mortality, the entire disease burden attributable to *Giardia* was from YERF. Therefore, adjustment for underreporting would have increased our estimate of YERF. However, 95% of the burden within the YERF calculation was from chronic giardiasis, and given the severity and duration of the symptoms associated with that health state, we expected that most would have been captured in the reported disease database. Adjusting the burden due to acute giardiasis (5% of YERF) would not have made a large difference in the overall HALY calculation.

4.5.6. *SHIGELLA*

Shigella are gram-negative bacteria that are spread by contaminated food and water, as well as from person to person. Shigellosis involves gastroenteritis (inflammation of the gastrointestinal tract) with severe diarrhea, fever, vomiting and abdominal pain. Profound dehydration, seizures, rectal bleeding, arthritis and kidney failure are potential complications of this disease. Treatment is focused on replacing salts and fluids, and antibiotics are given to severely ill individuals.

Data sources and HALY calculation

Since shigellosis is a reportable disease in Ontario, we calculated disease burden by using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to *Shigella*. For YERF, we extracted reported cases of shigellosis from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute infectious episode of gastroenteritis. Because reported cases underestimate the actual number of cases, we used a review article on the burden of shigella in industrialized and developing nations to quantify the underreporting of shigella.[133] Using the conservative estimate for industrialized nations from this paper, there were 20 shigella cases in the community for every reported case. We used epidemiologic studies to determine the duration of shigellosis.

Exhibit 4.42
Parameters for estimating the disease burden due to *Shigella*

Health State	Percentage of Reported Shigellosis Cases that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Gastroenteritis	100	1 week[134]	0.041	5,120

Estimated burden

We estimated annual averages of 0.33 deaths and 5,120 incident cases (256 before adjustment for underreporting) attributable to *Shigella*. Most of the disease burden was from premature mortality.

Limitations

Although we were able to adjust for underdiagnosis and underreporting of *Shigella*, the data used for the adjustment was not Canadian and may not accurately reflect the current trends of underreporting in Canada/Ontario. Furthermore, the validity of these estimates is dependent on the quality of the reportable disease data.

4.5.7. *E. COLI* O157:H7

E. coli O157:H7 is a strain of the bacterium *Escherichia coli* that causes gastroenteritis (inflammation of the gastrointestinal tract) leading to bloody diarrhea and abdominal pain. Transmission occurs from eating contaminated beef, water sources, vegetables and unpasteurized milk, as well as from person to person. It produces a verotoxin that can lead to kidney failure from hemolytic uremic syndrome (loss of red blood cell, platelet and kidney function from toxin damage), which is more common in children and the elderly. Antibiotics do not appear to improve the course of the disease and, in fact, may increase the risk of hemolytic uremic syndrome. In May 2000, 2,500 people in Walkerton, Ontario, were infected with *E. coli* O157:H7 through the municipal water system.[135]

The burden of most other strains of *E. coli* (i.e., non-O157:H7) is described in the common bacterial infections section. The O157:H7 strain differs from other strains in terms of the mode of transmission, potential interventions for prevention, data sources and severity of disease.

Data sources and HALY calculation

Since *E. coli* O157:H7 is a reportable disease in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to *E. coli* O157:H7 and hemolytic uremic syndrome. For YERF, we extracted reported cases of *E. coli* O157:H7 from Ontario's reportable disease database (iPHIS). Since reported cases may underestimate the actual number cases, we used a Canadian study by Thomas et al. that used data from multiple sources to quantify the underreporting of *E. coli* O157:H7.[126] Using the conservative estimate from this paper, there were 10 cases of *E. coli* O157:H7 in the community for every case that was properly diagnosed and reported. We used epidemiologic studies to determine the percentage of *E. coli* O157:H7 cases that progressed to the following health states: non-bloody diarrhea, bloody diarrhea, haemolytic ureamic syndrome and end-stage renal disease. Epidemiologic studies were also used to determine the duration of illness of each of the health states associated with E. *coli* O157:H7.

Exhibit 4.43

Parameters for estimating the disease burden due to *E. coli* O157:H7

Health State	Percentage of *E. coli* O157:H7 Cases in the Community that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Non-bloody diarrhea	54[38]	3 days[38]	0.041	1,694
Bloody diarrhea	46[38]	5 days[38]	0.086	1,492
Haemolytic ureamic syndrome	1.6[136]	1.5 weeks[137]	0.171	53
End-stage renal disease	0.35[138]	5 years	0.157	11

Estimated burden

We estimated annual averages of 0 deaths and 3,188 incident cases attributable to *E. coli* O157:H7. Disease burden was relatively equal between males and females and was evenly distributed among age groups. It should be noted that the data collection periods for both mortality and incidence did not coincide with the Walkerton outbreak of 2000. It is also important to clarify that this strain is not responsible for the major population burden of *E. coli* infection. Instead, it was endogenous *E. coli* strains (see section 4.1.2.) that were the fifth leading pathogen in Ontario, given that they are a major cause of urinary tract, bloodstream and other invasive bacterial infections.

Limitations

Although we were able to adjust for underdiagnosis and underreporting of *E. coli* O157:H7 based on a Canadian study, the validity of these estimates is dependent on the quality of the reportable disease data. Our methodology could not account for year-to-year fluctuations in infection. Of note, the large outbreak that occurred in Walkerton in 2000 was before our study period.

4.5.8. *YERSINIA ENTEROCOLITICA*

Yersinia enterocolitica (*Yersinia*) is a food-borne bacterium that produces gastroenteritis (inflammation of the gastrointestinal tract) causing severe diarrhea, abdominal pain, or less commonly, enlargement of abdominal lymph nodes causing mesenteric adenitis. The pain can be severe enough to mimic appendicitis, and individuals may be operated upon needlessly. Antibiotics are used to decrease the length and severity of the disease. Prevention is focused on hygiene and food safety.

Data sources and HALY calculation

Since yersiniosis is a reportable disease in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to *Yersinia*. For YERF, we extracted reported cases of yersiniosis from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute infectious episode of gastroenteritis. We used epidemiologic studies to determine the percentage of reported yersiniosis cases that progressed to mesenteric adenitis and the duration of each of these health states.

Exhibit 4.44
Parameters for estimating the disease burden due to *Yersinia enterocolitica* (*Yersinia*)

Health State	Percentage of Reported *Yersinia* Cases that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Gastroenteritis	100	17 days[139]	0.041	327
Mesenteric adenitis	8[140]	17 days[139]	0.086	26

Estimated burden

We estimated annual averages of 0 deaths and 327 incident cases attributable to *Yersinia*. The entire disease burden was from YERF. Disease burden was equally distributed between males and females and was mainly in individuals aged 0–14.

Limitations

These estimates for the burden of *Yersinia* are dependent on the quality of the reportable disease data; the limitations of these data are described in greater detail in Chapter 5. There is a high likelihood of underdiagnosis and underreporting that we were unable to adjust for because we could not find any epidemiologic studies with empirical data. However, because the HALY estimate for *Yersinia* was extremely small, adjusting for underreporting is unlikely to have an appreciable impact.

4.5.9. *CRYPTOSPORIDIUM*

Cryptosporidium is a protozoan parasite that dwells in the intestines of humans and other mammals. It is spread by contaminated food and water, as well as person-to-person contact. In normal hosts, it causes self-limited gastroenteritis (inflammation of the gastrointestinal tract) with diarrhea, abdominal pains, fever and cramps. Rarely, bloody diarrhea can occur. In people with pre-existing disease such as HIV, infection can result in pancreatitis (pancreas inflammation), chronic diarrhea, severe weight loss and dehydration. Antibiotics can be used, but most care revolves around symptoms. For HIV-infected patients, cure involves treatment of the underlying HIV. Vaccinations are not available, but urban water treatment plants are able to decrease the spread of disease.

Data sources and HALY calculation

Since cryptosporidiosis is a reportable disease in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to *Cryptosporidium*. For YERF, we extracted reported cases of cryptosporidiosis from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute infectious episode of gastroenteritis. We used epidemiologic studies to determine the duration of cryptosporidiosis.

Exhibit 4.45
Parameters for estimating the disease burden due to *Cryptosporidium*

Health State	Percentage of Reported *Cryptosporidium* Cases that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Gastroenteritis	100	12 days[141]	0.041	357

Estimated burden

We estimated annual averages of 0 deaths and 357 incident cases attributable to *Cryptosporidium*. The entire disease burden attributed to *Cryptosporidium* was the result of YERF. Disease burden was equally distributed between males and females and most affected the younger age groups (age 0–14).

Limitations

These estimates for the burden of *Cryptosporidium* are dependent on the quality of the reportable disease data; the limitations of these data are described in greater detail in Chapter 5. There is a high likelihood of underdiagnosis and underreporting that we were unable to adjust for because we could not find any epidemiologic studies with empirical data. However, because the HALY estimate for *Cryptosporidium* was extremely small, adjusting for underreporting is unlikely to have an appreciable impact. Note that *Cryptosporidium* manifestations vary significantly by host status; infection may cause only mild disease in healthy individuals but can cause protracted illness in HIV-affected individuals. Due to their rarity, more severe outcomes were not included. Our methodology is too coarse to differentiate illness according to patient characteristics.

4.5.10. *CYCLOSPORA CAYETENSIS*

Cyclospora cayetensis (*Cyclospora*) is a protozoan organism transmitted through contaminated food and water and is endemic in tropical and sub-tropical countries. *Cyclospora* infection produces gastroenteritis (inflammation of the gastrointestinal tract) which causes watery diarrhea, cramping, weight loss, abdominal bloating, fever and fatigue. Complications include severe dehydration requiring hospitalization. A seven-day course of antibiotics is given to clear the infection.

Data sources and HALY calculation

Since cyclosporiasis is a reportable disease in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to cyclospora. For YERF, we extracted reported cases of cyclosporiasis from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute infectious episode of gastroenteritis. We used epidemiologic studies to determine the duration of cyclosporiasis.

Exhibit 4.46
Parameters for estimating the disease burden due to *Cyclospora cayetensis* (*Cyclospora*)

Health State	Percentage of Reported *Cyclospora* Cases that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Gastroenteritis	100	3 weeks[142]	0.041	106

Estimated burden

We estimated annual averages of 0 deaths and 106 incident cases attributable to *Cyclospora*. The entire disease burden attributed to *Cyclospora* was the result of YERF. Disease burden was equally distributed between males and females and among all age groups.

Limitations

These estimates for the burden of *Cyclospora* are dependent on the quality of the reportable disease data; the limitations of these data are described in greater detail in Chapter 5. There is a high likelihood of underdiagnosis and underreporting that we were unable to adjust for because we could not find any epidemiologic studies with empirical data. However, because the HALY estimate for *Cyclospora* was extremely small, adjusting for underreporting is unlikely to have an appreciable impact on disease burden.

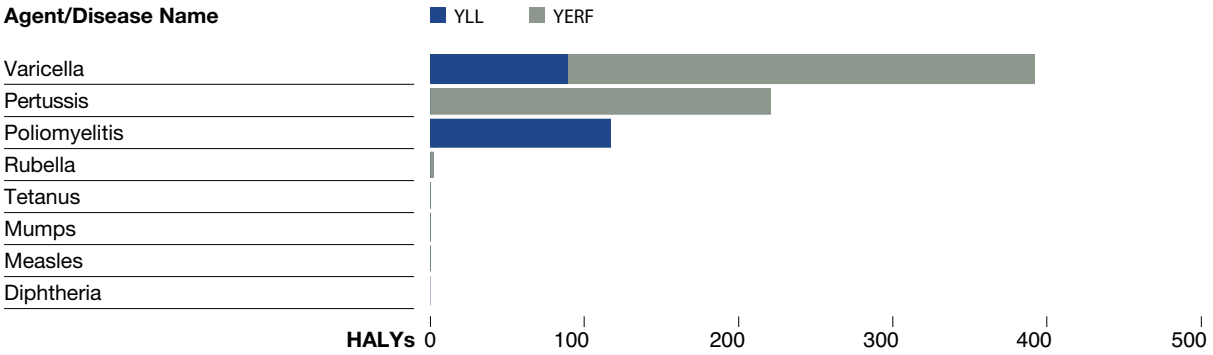
4.6 VACCINE-PREVENTABLE DISEASES

Infectious agents assigned to this disease group are diseases that are preventable with routine immunizations. Note that vaccines are routinely given in Ontario for a number of other pathogens that are considered in other sections of this report; they include *N. meningitidis*, *S. pneumoniae*, influenza, hepatitis B and HPV. All of the agents in this section are reportable diseases, but varicella zoster virus (VZV) is grossly underreported—many cases may not even come to medical attention—and therefore required a different methodological approach.

Within this disease group, the VZV accounted for the greatest burden (Exhibit 4.47). Five of the pathogens (mumps, measles, tetanus, rubella and diphtheria) had no appreciable burden, a reflection of the success of vaccination programs. Poliomyelitis was the only disease for which the burden varied by sex, with a much higher relative burden in females; the deaths were from the long-term sequelae of remote polio infection (Exhibit 4.48).

Exhibit 4.47

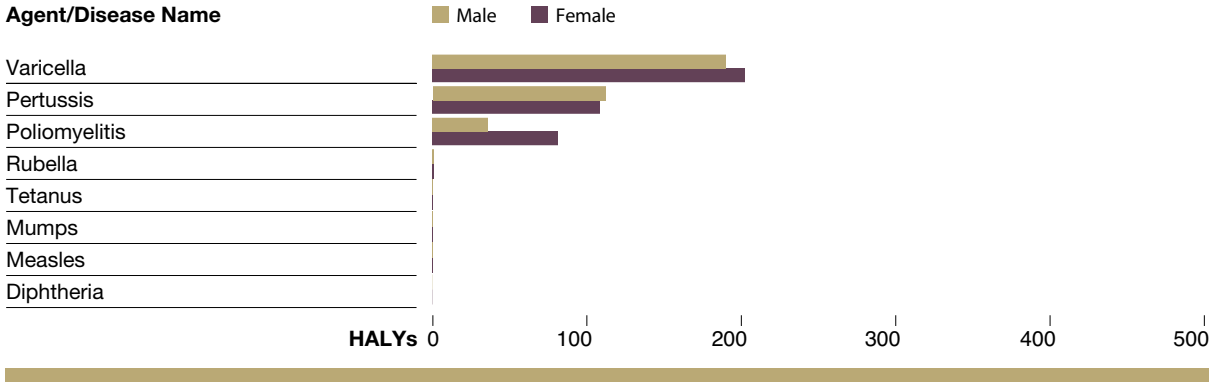
Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for vaccine-preventable diseases



Note: YLL for polio were due to long-term complications of polio rather than current infections.

Exhibit 4.48

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for vaccine-preventable diseases, by sex



4.6.1. VARICELLA ZOSTER VIRUS

Varicella zoster virus (VZV) has a human reservoir and is transmitted by respiratory droplets or airborne spread. After an incubation period of 10–21 days, varicella (chickenpox) develops; it is characterized by fever and itchy, fluid-filled blisters. Varicella can occasionally be complicated by pneumonia (lung infection), encephalitis (inflammation of the brain) or secondary bacterial skin and soft tissue infection such as cellulitis, and more rarely, necrotizing fasciitis (flesh-eating disease). The disease is more severe if acquired in adulthood and can result in congenital varicella if acquired in pregnancy. After varicella has resolved, the virus remains dormant for life in the nerve roots and can reemerge to cause herpes zoster (shingles) years later. Zoster is a painful rash in the distribution of a single nerve root and can be complicated by spread to other areas causing cellulitis, encephalitis, hepatitis (liver inflammation) and pneumonia. Some individuals with zoster will experience lifelong pain known as post-herpetic neuralgia. A vaccine is available to protect against varicella and is typically given at 15 months of age. A new vaccine to prevent zoster was approved for use in Canada in 2009.

Data sources and HALY calculation

Although varicella is a reportable disease in Ontario, physicians usually make a clinical diagnosis of the disease and rarely report it to public health officials. Additionally, zoster is not a reportable disease in Ontario. For these reasons, the burden of varicella zoster was calculated from health care utilization data. For YLL, we used Ontario vital statistics data to determine the number of deaths due to primary varicella, zoster and congenital varicella. For YERF, we used Ontario health care utilization data to determine the number of episodes of: acute varicella, varicella with complications, acute zoster and zoster with complications. Because we only used health care utilization data to capture cases of varicella and zoster, our data sources were missing cases in the community who did not seek medical attention. To account for this potential underestimation of varicella and zoster cases we adjusted for this underestimate using epidemiologic studies. A Canadian study by Law et al. estimated that only 40% of varicella cases see a doctor for their illness.[143] Therefore, for every case of varicella that seeks medical attention, there are actually 2.5 cases of varicella. The majority of zoster cases seek medical care, so this correction factor was not applied for zoster cases. We used epidemiologic studies to determine the duration of illness for each of these health states.

Exhibit 4.49
Parameters for estimating the disease burden due to varicella zoster virus

Health State	Duration	Severity Weight	Episode Length	Number of Episodes
Acute varicella episode	2 weeks[144]	0.023	3 years	66,055
Varicella with complications	4 days[145]	0.286	3 years	178
Acute zoster episode	1 month[146]	0.052	60 days	48,284
Zoster with complications	4 months[147]	0.068	60 days	1,532

Estimated burden

We estimated annual averages of 6 deaths and 116,049 health care utilization episodes attributable to VZV. The burden of VZV was relatively equally distributed between males and females. Disease burden was evenly distributed among age groups, as varicella contributed to burden in the younger age groups and zoster contributed to burden in the middle and older age groups.

Limitations

A limitation of these estimated burdens of VZV is that not all cases of varicella seek medical attention for their illness. Therefore, using only health care utilization data underestimates the true burden. However, we accounted for this limitation by adjusting for health care seeking behaviour among individuals infected with varicella. The limitations associated with the health care utilization data are described in greater detail in Chapter 5. Lastly, our data provide a static estimate of varicella zoster burden, but the epidemiology has been changing over time due to approval of varicella vaccines in Canada in 1998 and the implementation of a publicly funded immunization program in Ontario in 2004.[148] It is noteworthy that the impact of universal vaccination with poor coverage has the potential to decrease the population burden of VZV but also has the potential to increase the burden of disease in the future in several ways: the average age at infection may increase with an accompanying increase in disease severity; the increased age at infection may increase the number of congenital and neonatal cases of VZV; and, the reduced incidence may increase the burden of zoster through reduced natural boosting of the population.[149]

4.6.2. *BORDETELLA PERTUSSIS*

Bordetella pertussis (pertussis) is a gram-negative bacterium that causes pertussis (whooping cough). It is transmitted by respiratory droplets. It causes weeks of paroxysmal cough which can result in vomiting and may have characteristic whooping sound. Complications can include pneumonia (lung infection) and seizures. Mortality rates can be as high as 3% in infancy. Antibiotics can help shorten the disease length, severity, and transmissibility. A vaccine is offered during childhood with a booster in adolescence, and antibiotics are often given to close contacts to prevent infection.

Data sources and HALY calculation

Since pertussis is a reportable disease in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to pertussis. For YERF, we extracted reported cases of pertussis from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute infectious episode of pertussis. Since reported cases of pertussis underestimate actual cases of pertussis in the community, we used a Canadian study by Deeks et al. that used community surveys and physician records to quantify the underreporting of pertussis.[150] It was estimated that at that time there were 28.3 pertussis cases for every reported case. However, since the time of that study laboratory methods have become much more sensitive to the detection of pertussis. Based on expert opinion, we estimated that current laboratory methods were three times more sensitive during the ONBOIDS study period than when the aforementioned study was conducted. Therefore, we multiplied reported cases by a factor of 9.4 (28.3 divided by 3) to account for potential underreporting of pertussis. Epidemiologic studies were also used to determine the percentage of reported pertussis cases that progressed to pneumonia and to determine the duration of illness for each of these health states.

Exhibit 4.50
Parameters for estimating the disease burden due to *Bordetella pertussis* (pertussis)

Health State	Percentage of Reported Pertussis Cases per Year that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Acute infectious episode of pertussis	100	6 weeks[151]	0.041	8,874
Pneumonia	13 (infants <1 year old); 3 (all other ages)[152]	2 weeks[27]	0.136	451
Seizure disorder	1.5 (infants <1 year old); 0.45 (all other ages)[152]	Lifetime	0.039	59

Estimated burden

We estimated annual averages of 0 deaths and 8,874 incident cases attributable to pertussis. The burden of pertussis was relatively equal between males and females, and most of the burden was in children younger than four years of age.

Limitations

These estimates for the burden of pertussis are dependent on the quality of the reportable disease data; the limitations of these data are described in greater detail in Chapter 5. In addition to there likely being many symptomatic cases who do not seek medical care, there is a high likelihood of underdiagnosis and underreporting that we attempted to adjust for using data from a Canadian study. However, it is possible that the extent of underascertainment remains high, particularly in adolescents and adults, as well as vaccinated individuals, for whom the index of suspicion for pertussis infection is generally low. Therefore, these estimates likely underestimate the true burden of pertussis.

4.6.3. POLIOMYELITIS

Poliovirus is the virus responsible for poliomyelitis (also known as polio), and is spread by oral-fecal contact. After an incubation period of days to weeks, most children (95%) develop only asymptomatic infection. Five percent develop a brief episode of fever, headache and sore throat. More worrisome, one in 1,000 patients develops paralysis, with higher proportions in older patients. Many survivors of paralytic polio experience chronic muscle weakness and fatigue. There is no cure. Mass immunization programs have been successful in eliminating polio transmission, and the Americas have been certified as polio-free since 1994. Despite global polio-eradication commitment and effort, the disease remains endemic in four countries in the world.

Data sources and HALY calculation

Since poliomyelitis is a reportable disease in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to acute poliomyelitis and sequelae of poliomyelitis. For YERF, we searched for reported cases of poliomyelitis from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute infectious episode of poliomyelitis. We used epidemiologic studies to determine the percentage of reported poliomyelitis cases that developed paralysis and to determine the duration of illness for each of these health states.

Exhibit 4.51
Parameters for estimating the disease burden due to poliomyelitis

Health State	Percentage of Reported Poliomyelitis Cases per Year that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Acute infectious episode of poliomyelitis	100	10 days[153]	0.093	0
Paralysis	0.1[153]	Lifetime	0.089	0

Estimated burden

We estimated annual averages of eight deaths and no incident cases attributable to poliomyelitis. All of the recorded poliomyelitis deaths were due to the sequelae of poliomyelitis and not acute poliomyelitis; therefore, the burden of poliomyelitis is due to the sequelae of remote or imported polio infection. The burden was significantly higher in females; however, it is unknown if there is an epidemiologic reason for this difference or if this was due to chance alone. All of the disease burden affected individuals over the age of 45 and was distributed evenly among the older age groups.

Limitations

Since polio was eliminated from Canada in 1994,[154] the burden of polio determined in this study is from remote infection among immigrants to Canada, and therefore does not represent the burden expected with a true "incidence-based approach" (i.e., expected morbidity and mortality from polio in the future arising from current incidence of polio infections).

4.6.4. RUBELLA

The rubella virus is responsible for causing rubella (German measles), as well as congenital rubella syndrome (CRS) in newborns. The virus is transmitted by respiratory droplets or *in utero* from mother to child. Typically, the infected individual will experience a rash, fever, swollen glands, joint pains, headaches and conjunctivitis. There is no specific treatment available for rubella, but a vaccination series is provided to children. If acquired by newborns during pregnancy, CRS can result, which is associated with defects with the heart, brain, eyes and ears. Pregnant women are also screened for rubella immunity.

Data sources and HALY calculation

Since rubella and CRS are reportable diseases in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to rubella and CRS. For YERF, we searched for reported cases of rubella from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute infectious episode of rubella. We used epidemiologic studies to determine the percentage of reported rubella cases that progressed to CRS and to determine duration of illness for an each health state.

Exhibit 4.52
Parameters for estimating the disease burden due to rubella

Health State	Percentage of Reported Rubella Cases per Year that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Acute infectious episode of rubella	100	10 days[28]	0.023	105
Congenital rubella syndrome	1.3	Lifetime	0.023	1

Estimated burden

We estimated annual averages of 0 deaths and 105 incident cases attributable to rubella (including CRS). There were no differences in the burden of rubella between males and females, and most of the disease burden impacted individuals aged 5–19. The vast majority of rubella cases were due to an outbreak in 2005.

Limitations

These estimates for the burden of rubella are dependent on the quality of the reportable disease data; the limitations of these data are described in greater detail in Chapter 5. There is a high likelihood of underdiagnosis and underreporting that we were unable to adjust for because we could not find any epidemiologic studies with empirical data. However, because the HALY estimate for rubella was extremely small, adjusting for underreporting is unlikely to have an appreciable impact.

4.6.5. MUMPS

The mumps virus causes fever and parotitis (inflammation of the parotid gland). It can lead to orchitis (inflammation of the testicle) in post-pubertal men. It is spread by respiratory secretions from infected individuals. It can cause complications such as infertility, pancreatitis, meningitis (cerebrospinal fluid infection), hearing loss and encephalitis (inflammation of the brain). There is no specific treatment, but a series of vaccinations are available in childhood.

Data sources and HALY calculation

Since mumps is a reportable disease in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to mumps. For YERF, we searched for reported cases of mumps from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute infectious episode of mumps. We used epidemiologic studies to determine the percentage of reported mumps cases that progressed to orchitis, deafness, meningitis and encephalitis and to determine the duration of illness for each of these health states.

Exhibit 4.53
Parameters for estimating the disease burden due to mumps

Health State	Percentage of Reported Mumps Cases per Year that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Acute infectious episode of mumps	100	10 days[155]	0.023	26
Orchitis (men only)	15[156]	1 week[27]	0.039	2
Meningitis	5[155]	2 weeks[27]	0.652	1
Encephalitis	5 in 1,000 cases (0.5%)[156]	3 weeks[109]	0.502	0
Deafness	1 in 20,000 cases (0.005%)[157]	Lifetime[157]	0.071	0

Estimated burden

We estimated annual averages of 0 deaths and 26 incident cases attributable to mumps. There were no differences in disease burden between males and females, and the vast majority of disease burden affected those aged 15–44.

Limitations

These estimates for the burden of mumps are dependent on the quality of the reportable disease data; the limitations of these data are described in greater detail in Chapter 5. There is a high likelihood of underdiagnosis and underreporting that we were unable to adjust for because we could not find any epidemiologic studies with empirical data. However, because the HALY estimate for mumps was extremely small, adjusting for underreporting is unlikely to have an appreciable impact. Our methodology is unable to capture the dynamic nature of mumps epidemiology and will underestimate burden as mumps outbreaks continue to occur, the most recent of which occurred in 2009–2010, outside of the study period.

4.6.6. *CLOSTRIDIUM TETANI*

Clostridium tetani (tetanus) is a rod shaped gram-positive bacterium that causes tetanus. Tetanus can occur after bacterial spores enter the body through wounds caused by contaminated objects. They release a toxin in the body that causes muscles to contract in involuntary and prolonged spasms. These actions can compromise the patient's airway and blood pressure, and the mortality rate can be higher than 11%. A vaccine series is offered during childhood, and booster vaccines are provided during adulthood or given along with tetanus immunoglobulin after a high-risk exposure.

Data sources and HALY calculation

Since tetanus is a reportable disease in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to tetanus. For YERF, we searched for reported cases of tetanus from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute episode of tetanus. We used epidemiologic studies to determine the duration of illness for an acute episode of tetanus.

Exhibit 4.54
Parameters for estimating the disease burden due to *Clostridium tetani* (tetanus)

Health State	Percentage of Reported Tetanus Cases per Year that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Acute episode of tetanus	100	5 weeks[158]	0.724	1

Estimated burden

We estimated annual averages of 0 deaths and one incident case attributable to tetanus.

Limitations

These estimates for the burden of tetanus are dependent on the quality of the reportable disease data; the limitations of these data are described in greater detail in Chapter 5. There is the possibility of underdiagnosis and underreporting that we were unable to adjust for because we could not find any epidemiologic studies with useful empirical data. However, since tetanus is generally a severe infection, the majority of tetanus cases would have sought medical attention and been reported.

4.6.7. MEASLES

The measles virus (previously called rubeola) causes a respiratory infection that is transmitted by respiratory droplets and airborne spread. It is one of the most infectious of all known pathogens. Measles infection is characterized by cough, fever, red eyes and extensive rash. Complications of the infection include diarrhea, pneumonia and early or delayed encephalitis (inflammation of the brain). There is no cure and treatment is symptomatic, but vaccinations are provided to children during their second year of life.

Data sources and HALY calculation

Since measles is a reportable disease in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to measles. For YERF, we searched for reported cases of measles from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute infectious episode of measles. We used epidemiologic studies to determine the percentage of reported measles cases that progressed to otitis media, pneumonia and encephalitis, and to determine the duration of illness for each of these health states.

Exhibit 4.55
Parameters for estimating the disease burden due to measles

Health State	Percentage of Reported Measles Cases that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Acute infectious episode of measles	100	10.5 days[28]	0.157	3
Otitis media	6.6[159]	4.5 days[45]	0.052	0
Pneumonia	6.5[159]	2 weeks[27]	0.136	0
Encephalitis	0.1[159]	3 weeks[109]	0.502	0

Estimated burden

We estimated annual averages of 0 deaths and 3 incident cases attributable to measles. There were no differences in disease burden between males and females, and the vast majority of disease burden affected children aged 0–4 years.

Limitations

These estimates for the burden of measles are dependent on the quality of the reportable disease data; the limitations of these data are described in greater detail in Chapter 5. There is the possibility of underdiagnosis and underreporting that we were unable to adjust for because we could not find any epidemiologic studies with empirical data. However, because the HALY estimate for mumps was extremely small, adjusting for underreporting is unlikely to have an appreciable impact. Our methodology could not account for year-to-year fluctuations in measles. It should be noted that the most recent measles outbreak in 2008 occurred after our study period.

4.6.8. *CORYNEBACTERIUM DIPHTHERIAE*

Corynebacterium diphtheriae (diphtheria) is the bacterium responsible for causing diphtheria. It has a human reservoir and is spread by physical contact or inhaling contaminated droplets. Diphtheria causes a fever and pharyngitis (sore throat); a membrane that forms over the throat and tonsils can make it difficult to swallow. The bacteria can produce a toxin, and complications include nerve paralysis and myocarditis (heart inflammation). Antitoxins are available and a vaccine series to prevent infection is offered in childhood with boosters in adolescence and adulthood.

Data sources and HALY calculation

Since diphtheria is a reportable disease in Ontario, we calculated disease burden using an agent-based approach. For YLL, we used Ontario vital statistics data to determine the number of deaths due to diphtheria. For YERF, we searched for reported cases of diphtheria from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute infectious episode of diphtheria. We used epidemiologic studies to determine the percentage of reported diphtheria cases that would have developed neurological complications and to determine duration of illness for an each health state.

Exhibit 4.56
Parameters for estimating the disease burden due to *Corynebacterium diphtheriae* (diphtheria)

Health State	Percentage of Reported Diphtheria Cases per Year that Progress to Each Health State	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Acute infectious episode of diphtheria	100	12 days[160]	0.041	0
Neurological complications	10	6 months	0.039	0

Estimated burden

We estimated annual averages of 0 deaths and 0 incident cases attributable to diphtheria.

Limitations

These estimates for the burden of diphtheria are dependent on the quality of the reportable disease data; the limitations of these data are described in greater detail in Chapter 5. There is the possibility of underdiagnosis and underreporting that we were unable to adjust for because we could not find any epidemiologic studies with empirical data. The term diphtheria refers to a specific and severe syndrome. The organism that causes this syndrome can also cause milder infections which present as a simple pharyngitis. Such infections have been detected in Ontario every couple of years (data from the Ontario Public Health Laboratory) in some communities. These do not represent a significant burden of disease but indicate that the causative organism continues to circulate in a limited way in the population, that we may find more of it if we look harder, and that improvements in coverage in some underimmunized communities may be warranted. The importance of continued vigilance has been shown by the epidemics of diphtheria which occurred in the former USSR in the 1990s.[161]

4.7 *MYCOBACTERIUM TUBERCULOSIS*

Mycobacterium tuberculosis (TB) is a bacterium transmitted almost exclusively by the airborne route. Primary disease may develop, typically within two years of initial exposure, or post-primary disease may arise years to decades later through reactivation of latent (dormant) infection. An estimated one in three people in the world have latent infection with TB, but only a minority (5–10%) will go on to develop disease from TB later in life. The most common manifestation is pulmonary (lung) disease, and patients with this form of illness are potentially contagious. However, TB is also capable of causing disease in almost any other organ system (extra-pulmonary). The treatment of TB requires combination anti-tuberculosis drugs for at least six months. Upon diagnosis of pulmonary TB, patients are often placed in isolation for the first several weeks of anti-tuberculosis drug treatment to prevent the spread of infection to others.

Data sources and HALY calculation

Since TB is a reportable disease in Ontario, we used an agent-based approach to calculate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to TB disease, sequelae of TB disease, and congenital TB. For YERF, we extracted reported cases of TB disease from Ontario's reportable disease database (iPHIS). Using the Public Health Agency of Canada's 2006 report *Tuberculosis in Canada*, TB disease was categorized into three states (pulmonary, extra-pulmonary-non-lymph node, and extra-pulmonary-lymph node).[162] Cases with disease at multiple sites (i.e., pulmonary and extra-pulmonary) were considered in pulmonary TB group only, as the most severe health state. The pulmonary TB state was further divided to include: 1) pre-diagnosis and treatment (pre-treatment and contagious); 2) treatment in isolation (ongoing treatment and contagious); and 3) treatment out of isolation (ongoing treatment and not contagious). Individuals with pulmonary TB progressed through each of these states. We used epidemiologic studies to estimate the proportion of TB cases in each of these health states and the average duration of time spent in each state.

Exhibit 4.57
Parameters for estimating the disease burden due to *Mycobacterium tuberculosis* (TB)

Health State	Percentage of Reported TB Cases Per Year by Health State (%I)	Duration	Severity Weight	Number of Cases Expected to Develop Health State
Pulmonary TB	58[162]			391
Prior to diagnosis and treatment		50 days	0.070	
Treatment in isolation		3 weeks	0.175	
Treatment out of isolation		200 days	0.023	
Extra-pulmonary TB – non-lymph node	27[162]	5 weeks	0.023	182
Extra-pulmonary TB – lymph node	15[162]	2 months	0.086	101

Estimated burden

Using the methods outlined we calculated 647 YLL and 16 YERF, resulting in 662 HALYs. We estimated annual averages of 673 incident cases of TB and 41 deaths attributable to TB. Most of the disease burden due to TB was from premature mortality. The burden of TB was slightly higher in males, as there were both more TB deaths and incident cases in males. Most of the disease burden due to TB was in individuals over the age of 40 years, where it was fairly evenly distributed by age.

Limitations

These estimates for the burden of TB are dependent on the quality of the reportable disease data; the limitations of these data are described in greater detail in Chapter 5. Although the possibility of underdiagnosis and underreporting exists, as a provincially reportable disease that typically causes persistent and progressive illness if untreated, it is assumed that most cases of TB disease are eventually detected and reported. It should be noted that for TB more than some other infections the relationship between today's incident cases and future morbidity and mortality is not straightforward, with disease reactivation, the increasing prevalence of immunocompromised individuals, and the emergence of multi-drug resistance impacting future disease burden; these dynamics are not captured in this cross-sectional analysis. As a majority of TB disease in Ontario occurs in foreign-born persons, future provincial trends will be highly dependent upon immigration patterns and trends. We also did not capture the burden beyond the individuals with TB disease (i.e., the impact on families and/or other contacts who are subjected to contact tracing and investigation). Lastly, TB is an example of a disease which is not evenly distributed around the province. Although a substantial proportion of the TB disease burden in Ontario affects foreign-born and homeless populations living in and around large urban centres, our study methodology does not explicitly define the intra-provincial distribution of TB disease burden.

4.8 MYCOSES

Most fungal infections are superficial (limited to outermost layer of the skin and hair) or cutaneous (extend deeper into the epidermis). However, some infections can become invasive and cause serious illness. Infectious agents assigned to this disease group are the most common fungal infections causing invasive disease. None of the mycoses are reportable diseases, so health care utilization data were used to estimate the burden of these agents.

Within this disease group, *Candida* had the highest disease burden followed by *Pneumocystis* and *Aspergillus* (Exhibit 4.58). The burden of *Candida* was slightly higher in females, and the burden of *Aspergillus* and *Blastomyces* was much higher in males (Exhibit 4.59).

Exhibit 4.58

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for mycoses

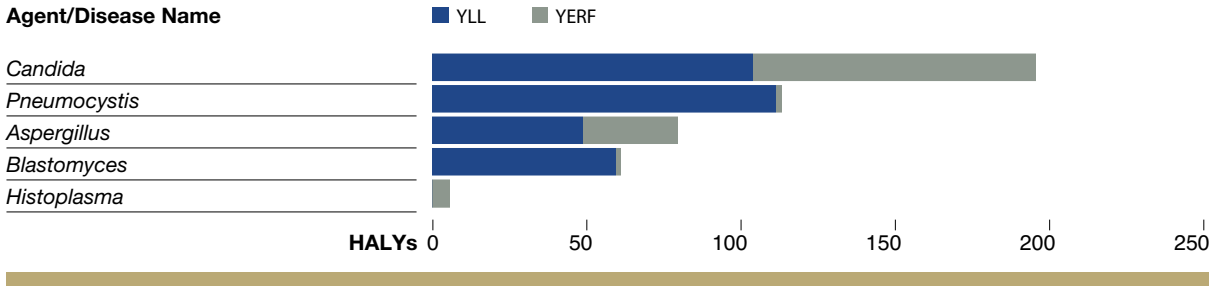
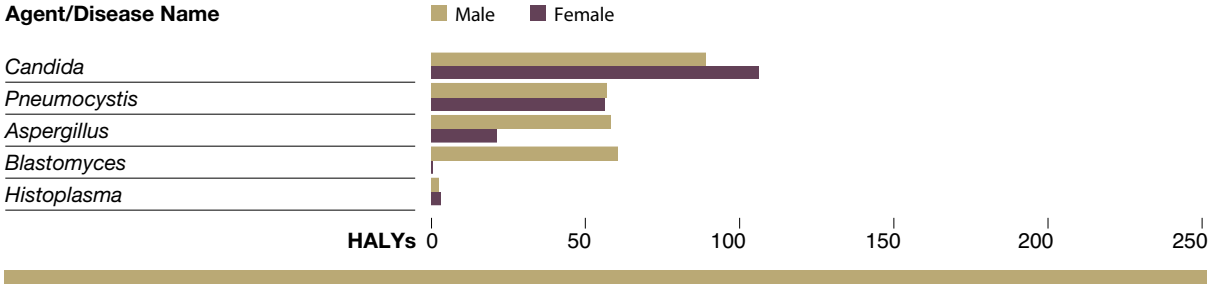


Exhibit 4.59

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for mycoses, by sex



4.8.1. *CANDIDA*

Candida is a yeast which is a normal component of skin and gastrointestinal flora. Most infections are endogenous (from the patient's own flora) with risk factors including antibiotic use, hospitalization, gastrointestinal surgery, indwelling catheters, prosthetic devices and immunocompromising conditions in the host. *Candida* can cause mild, non-invasive infections of mucosal surfaces, such as oral thrush, vaginal candidiasis and diaper rash. Semi-invasive syndromes such as esophagitis and enteritis require systemic treatment, and invasive syndromes such as septicaemia, endocarditis and meningitis are relatively rare and are associated with high mortality rates.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to non-invasive candidiasis, semi-invasive candidiasis and invasive candidiasis. For YERF, we used Ontario health care utilization data to determine the number of episodes of non-invasive, semi-invasive and invasive candidiasis. We used epidemiologic studies to determine the duration of illness for each health state.

Exhibit 4.60
Parameters for estimating the disease burden due to *Candida*

Health State	Duration	Severity Weight	Episode Length	Number of Cases Expected to Develop Health State
Candidiasis – non-invasive	2.5 weeks[163]	0.023	30 days	70,625
Candidiasis – semi-invasive	1 week[163]	0.052	3 years	815
Candidiasis – invasive	40 days[163]	0.652	3 years	176

Estimated burden

We estimated annual averages of 7 deaths and 71,616 health care utilization episodes attributable to *Candida*. The burden of *Candida* was relatively equal between males and females. It should be noted that there were nearly twice as many incident cases of non-invasive candidiasis in females. However, the increased burden of non-invasive candidiasis cases in females was offset by there being twice as many deaths due to *Candida* in males. Disease burden was distributed fairly equally among age groups with the exception of the 5-14 age group which had no burden. The burden due to incident cases in younger individuals was balanced by the burden from deaths due to *Candida* in older individuals.

Limitations

These estimates for the burden of *Candida* are limited by the sources of uncertainty arising from symptomatic cases not seeking medical attention and, therefore, not being captured in the health utilization data, as well as the data quality issues associated with the health care utilization data. Another limitation is that these estimates change over time and there is an increasing incidence of invasive candidial infections.[164] This is because invasive disease is most common in immuncompromised individuals and through nosocomial acquisition, two situations which have also been increasing over time.[164, 165]

4.8.2. *PNEUMOCYSTIS JIROVECI*

Pneumocystis jiroveci (PCP) was previously believed to be a parasite, but has been reclassified as a fungus. This organism only causes infection among patients with severe deficiencies in cell mediated immunity such as that associated with advanced HIV infection, organ transplantation and high dose steroid therapy. Patients typically present with an insidious onset of fever, shortness of breath and nonproductive cough. Trimethoprim-sulfamethoxazole is the treatment of choice, and is also used as prevention in high risk patient populations.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to pneumocystosis. For YERF, we used Ontario health care utilization data to determine the number of episodes of pneumocystosis. We used epidemiologic studies to determine the duration of illness for pneumocystosis.

Exhibit 4.61
Parameters for estimating the disease burden due to *Pneumocystis jiroveci*

Health State	Duration	Severity Weight	Episode Length	Number of Episodes
Pneumocytosis	4 weeks[166]	0.136	3 years	177

Estimated burden

We estimated annual averages of four deaths and 177 health care utilization episodes attributable to *Pneumocystis*. The vast majority of disease burden attributed to pneumocystis was due to YLL. The burden of *Pneumocystis* was relatively equal between males and females and distributed fairly evenly among age groups, with the exception of individuals aged 5–29 who had no disease burden.

Limitations

These estimates for the burden of *Pneumocystis* are limited by the sources of uncertainty arising from symptomatic cases not seeking medical attention and, therefore, not being captured in the health utilization data, as well as the data quality issues associated with the health care utilization data. However, the vast majority of disease burden due to *Pneumocystis* was from YLL and not YERF. Since adjustment for propensity to seek medical treatment would only affect the YERF calculation, and YERF contributed very little to the overall disease burden, it is unlikely that adjustment would have significantly changed the estimate of disease burden.

4.8.3. *ASPERGILLUS*

Aspergillus is an environmental mold which can occasionally produce disease in normal hosts, but more commonly infects patients with underlying structural lung disease or systemic immunodeficiency associated with hematologic malignancies and chemotherapy-induced neutropenia. Lung involvement can be non-invasive, but in immunocompromised patients is usually invasive and associated with mortality rates exceeding 50%. Other invasive syndromes (e.g., central nervous system, sinus disease) are also associated with significant morbidity and mortality.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to non-invasive aspergillosis, pulmonary invasive aspergillosis, and non-pulmonary invasive aspergillosis. For YERF, we used Ontario health care utilization data to determine the number of episodes of non-invasive aspergillosis, pulmonary invasive aspergillosis and non-pulmonary invasive aspergillosis. We used epidemiologic studies to determine the duration of illness for each health state.

Exhibit 4.62
Parameters for estimating the disease burden due to *Aspergillus*

Health State	Duration	Severity Weight	Episode Length	Number of Episodes
Aspergillosis – non-invasive	3 months[167]	0.136	3 years	189
Aspergillosis – pulmonary invasive	1 year[27]	0.398	3 years	23
Aspergillosis –non-pulmonary invasive	1 year[27]	0.652	3 years	23

Estimated burden

We estimated annual averages of three deaths and 235 health care utilization episodes attributable to *Aspergillus*. Disease burden due to *Aspergillus* is higher in males, which can be attributed to more recorded *Aspergillus* deaths among males; however, it is unknown if there is an epidemiologic reason for this difference or if it is due to statistical chance. Most of the disease burden was among individuals over the age of 45.

Limitations

These estimates for the burden of *Aspergillus* are limited by the sources of uncertainty arising from symptomatic cases not seeking medical attention and, therefore, not being captured in the health utilization data, as well as the data quality issues associated with the health care utilization data. However, due to the severity and duration of the symptoms due to aspergillosis, most infected individuals would have sought medical treatment. Fatalities due to *Aspergillus* will be underestimated because our source of mortality data only listed a single cause of death, and because diagnostic testing for *Aspergillus* has low sensitivity. Most cases of *Aspergillosis* occur in patients with severe underlying lung disease or immunodeficiency, and deaths hastened by *Aspergillus* may have been coded according to the underlying disease which predisposed to *Aspergillus* infection.

4.8.4. *BLASTOMYCES*

Blastomyces is a dimorphic fungus (mold form in environment, yeast form in human host) which can infect both normal and immunocompromised hosts. It exists in nature in warm moist soil and decaying vegetation, and is endemic in Canadian areas that border the Great Lakes. The infection is usually acquired by inhalation, and the most common manifestation of blastomycosis is chronic pulmonary (lung) infection. However, dissemination can occur to skin, bones, joints, the genitourinary tract and the central nervous system. Treatment requires prolonged antifungal therapy.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to pulmonary blastomycosis and disseminated blastomycosis. For YERF, we used Ontario health care utilization data to determine the number of episodes of pulmonary blastomycosis and disseminated blastomycosis. We used epidemiologic studies to determine the duration of illness for each health state.

Exhibit 4.63
Parameters for estimating the disease burden due to *Blastomyces*

Health State	Duration	Severity Weight	Episode Length	Number of Episodes
Blastomycosis – pulmonary	2 months[168]	0.136	3 years	46
Blastomycosis – disseminated	6 months[169]	0.136	3 years	9

Estimated burden

We estimated annual averages of two deaths and 55 health care utilization episodes attributable to *Blastomyces*. The vast majority of disease burden attributed to blastomycosis was from premature mortality. Almost the entire disease burden of *Blastomyces* was among males as all six observed deaths over the three-year period occurred in males. This is in keeping with a prior epidemiologic study in Ontario that suggested that the majority (2/3) of cases of blastomycosis occurred in males.[170] Most of the disease burden was in individuals aged 25–49.

Limitations

These estimates for the burden of *Blastomyces* are limited by the sources of uncertainty arising from symptomatic cases not seeking medical attention and, therefore, not being captured in the health utilization data, as well as the data quality issues associated with the health care utilization data. However, the vast majority of disease burden due to *Blastomyces* was a result of YLL and not YERF. Since adjustment for propensity to seek medical treatment would only affect the YERF calculation, and YERF contributed very little to the overall disease burden, it is unlikely that adjustment would have significantly changed the estimate of disease burden. Moreover, our data are similar to the results of a previous laboratory based surveillance study in Ontario which identified 309 cases over a 10-year period from 1994–2003.[170] Additionally, blastomycosis is an example of a disease which would not be expected to be evenly distributed around the province. Our study methodology has not included an attempt to define the intra-provincial distribution of this disease burden.

4.8.5. *HISTOPLASMA*

Histoplasma is a dimorphic fungus (mold form in environment, yeast form in human host) that can infect both normal and immunocompromised hosts. It exists in nature in soil and in bird and bat guano. Although cases have been reported from every continent, the areas of highest endemnicity include the Ohio and Mississippi river vallies. In Canada, infection is most common in the region of the St. Lawrence River. The infection is usually acquired by inhalation, and the most common manifestation is pulmonary (lung) infection. However, disseminated infection is common in immunocompromised patients.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to histoplasmosis. For YERF, we used Ontario health care utilization data to determine the number of episodes of *histoplasmosis*. We used epidemiologic studies to determine the duration of illness for *histoplasmosis*.

Exhibit 4.64
Parameters for estimating the disease burden due to *Histoplasma*

Health State	Duration	Severity Weight	Episode Length	Number of Episodes
Histoplasmosis	2 months[171]	0.136	3 years	245

Estimated burden

We estimated annual averages of 0 deaths and 245 health care utilization episodes attributable to *Histoplasma*. Since there were no recorded histoplasma deaths, the entire disease burden attributed to histoplasma was due to YERF. The burden of *Histoplasma* was relatively equal between males and females and was distributed fairly equally among age groups, peaking in individuals aged 30–59.

Limitations

These estimates for the burden of *Histoplasma* are limited by the sources of uncertainty arising from symptomatic cases seeking medical attention and, therefore, not being captured in the health care utilization data, as well as the data quality issues associated with the health care utilization data. Histoplasmosis is particularly prone to underdiagnosis because most infections are self-limited and not all infections need to be treated. Histoplasmosis is an example of a disease which would not be expected to be evenly distributed around the province. Our study methodology has not included an attempt to define the intra-provincial distribution of this disease burden.

4.9. VECTOR-BORNE AND IMPORTED INFECTIONS

Infectious agents assigned to this disease group are mostly infections that occur outside of Ontario and brought into the province by infected individuals (mainly people travelling to or emigrating from areas where the disease is endemic), with the exception being West Nile virus (WNV), which was introduced to Ontario in 2001. Except for dengue, all the diseases included in this disease group are reportable in Ontario.

Within this disease group, West Nile virus (WNV) had the highest disease burden, followed by dengue and malaria (Exhibit 4.65). The burden of malaria and WNV was mostly in males, and the burden of dengue was almost entirely in females, but these proportions must be interpreted with caution given low event rates (Exhibit 4.66).

Exhibit 4.65

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for imported infections

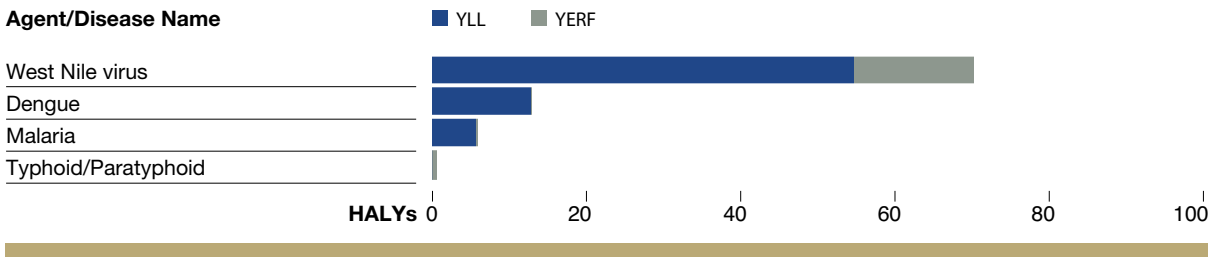
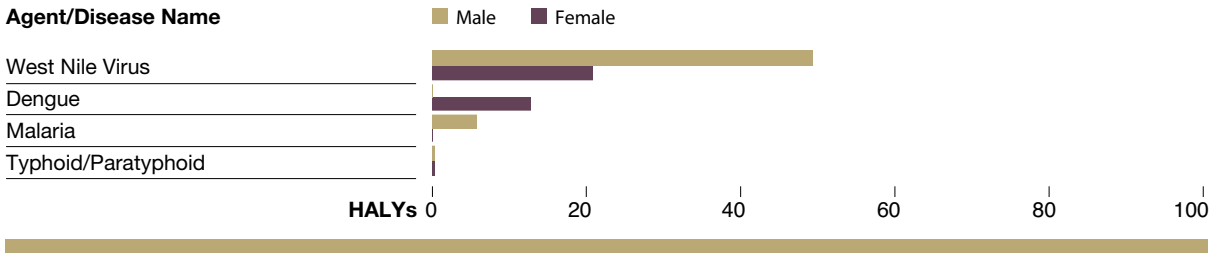


Exhibit 4.66

Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for imported infections, by sex



4.9.1. WEST NILE VIRUS

West Nile virus (WNV) is a mosquito-borne virus that is asymptomatic in the majority of cases but results in a febrile illness in 20% of patients and central nervous system involvement in approximately 0.7% of patients. Neurologic involvement can range from meningitis to encephalitis, myelitis and even polio-like syndromes.

Data sources and HALY calculation

Since WNV is a reportable disease in Ontario, we used an agent-based approach to calculate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to WNV infection. For YERF, we extracted reported cases of WNV illness from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute episode of West Nile fever. We used epidemiologic studies to determine the percentage of reported WNV cases that presented with neuroinvasive disease and what percentage of these neurological cases had long-term complications and to determine the duration of illness for each health state.

Exhibit 4.67
Parameters for estimating the disease burden due to West Nile virus (WNV)

Health State	Percentage of reported WNV cases per year that progress to health state	Duration	Severity weight	Number of cases expected to develop health state
West Nile fever	100	5 days[172]	0.023	50
West Nile – neuroinvasive disease	40[173]	3 weeks[27]	0.239	20
West Nile – long-term neurological complications	8[174]	Permanent	0.111	4

Estimated burden

We estimated annual averages of four deaths and 50 incident cases from West Nile virus. Most of the disease burden attributed to WNV was a result of YLL to premature mortality. The burden of WNV was higher in males, because the majority of WNV deaths occurred in males. Since the majority of WNV deaths occur in the elderly, disease burden mostly affects individuals aged 65 and older.

Limitations

These estimates for the burden of WNV are limited by the sources of uncertainty arising from symptomatic cases not seeking medical attention or from physicians failing to consider a diagnosis of WNV among symptomatic cases presenting with fever. There are also data quality issues associated with the reportable disease and laboratory data.

However, the vast majority of disease burden due to WNV was a result of YLL and not YERF. Since adjustment for underreporting would only affect the YERF calculation, and YERF contributed very little to the overall disease burden, it is unlikely that adjustment for underreporting would have significantly changed the estimate of disease burden. WNV exemplifies a major limitation of our methodology, in that we are deriving our data from a relatively brief three year time period, and infectious diseases are dynamic, with burdens that can shift greatly over time. Prior to 2001 WNV was non-existent in Ontario. After a few summers with many Ontario cases, we have seen far lower disease activity.

4.9.2. DENGUE

Dengue is a virus transmitted by mosquitoes in tropical climates. After a short incubation period of less than one week, dengue classically induces a febrile illness associated with severe muscle pains. In endemic areas, repeat dengue infection can result in dengue hemorrhagic fever, characterized by fever, bleeding, thrombocytopenia (low platelet count), vasculitis (inflammation of blood vessels) and shock (but this manifestation is fortunately rare among travelers). Treatment is supportive.

Data sources and HALY calculation

Since dengue is not a reportable disease in Ontario, we used a syndrome-based approach to calculate disease burden where all episodes/deaths of a syndrome were attributed to only dengue and no other pathogen. For YLL, we used Ontario vital statistics data to determine the number of deaths due to dengue fever (classical dengue) and dengue haemorrhagic fever. For YERF, we used Ontario health care utilization data to determine the number of episodes of dengue fever (classical dengue) or dengue haemorrhagic fever. There were so few episodes of dengue haemorrhagic fever that we combined episodes from both syndromes into a single health state called "dengue fever". We used epidemiologic studies to determine the duration of dengue fever.

Exhibit 4.68
Parameters for estimating the disease burden due to dengue

Health state	Duration	Severity Weight	Episode Length
Dengue fever	1 week[27]	0.348	3 years

Estimated burden

We estimated annual averages of 0.33 deaths and 14 incident cases (all cases of dengue fever) from dengue. Since there were so few incident cases of dengue, the vast majority of disease burden attributed to dengue was a result of YLL to premature mortality. However, there was only one death in the entire study period due to dengue. More years of study would need to be added in order to establish age and sex trends of the disease burden of dengue.

Limitations

These estimates for the burden of dengue are limited by the sources of uncertainty arising from symptomatic cases not seeking medical attention and, therefore, not being captured in the health utilization data, as well as the data quality issues associated with the health care utilization data. The symptoms of dengue fever are quite severe, and it was expected the majority of individuals infected would seek medical care. However, many physicians might not order diagnostic serology testing because they do not suspect this agent, or because the results of serology are often delayed (and usually only available after the patient's clinical illness has resolved). Dengue also exemplifies the difficulty in precisely estimating disease burden for infections with low case fatality rates. Fatal dengue infections are rare among travelers, and the one fatality present in our data (by chance) gives the impression that dengue disease burden is greater than malaria disease burden, when likely the opposite is true.

4.9.3. MALARIA

Malaria is a protozoal parasite transmitted by mosquitoes in tropical climates, which infests human red blood cells. The disease is typically characterized by cyclical fever, pain, and anemia. Cases caused by *Plasmodium falciparum* (one of five malarial species), can produce a range of severe complications including respiratory failure, confusion, seizures, renal (kidney) failure, jaundice, hypoglycemia and shock. However, with effective anti-malarial medications the case fatality ratio remains less than 1% among travelers returning to industrialized countries.

Data sources and HALY calculation

Since malaria is a reportable disease in Ontario, we used an agent-based approach to calculate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to malarial infection and congenital malaria. For YERF, we extracted reported cases of malaria from Ontario's reportable disease database (iPHIS). Data from the Public Health Laboratory of Ontario (where 75% of reported malaria cases in Ontario are confirmed) were used to determine what percentage of reported malarial infections was: *P. falciparum* positive with non-severe symptoms, *P. falciparum* positive with severe symptoms, and *P. falciparum* negative. Expert opinion was used to determine the duration of each type of malaria.

Exhibit 4.69
Parameters for estimating the disease burden due to malaria

Health state	Percentage of Reported Malaria Cases per Year that Progress to Health State	Duration	Severity Weight
Plasmodium falciparum – positive with non-severe symptoms	59	1 week	0.023
Plasmodium falciparum – positive with severe symptoms	7	18 days	0.174
Plasmodium falciparum – negative	34	1 week	0.023

Estimated burden

We estimated annual averages of 0.33 deaths and 183 incident cases (108 cases were expected to be *P. falciparum* positive with non-severe symptoms, 13 were expected to be *P. falciparum* positive with severe symptoms and 62 were expected to be *P. falciparum* negative from malaria). The vast majority of disease burden attributed to malaria was a result of premature mortality. However, there was only one death in the entire study period due to malaria.

Limitations

These estimates for the burden of malaria are limited by the sources of uncertainty arising from symptomatic cases not seeking medical attention or from physicians failing to consider a diagnosis of malaria or failing to collect specimens for laboratory testing among symptomatic cases. There are also data quality issues associated with the reportable disease and laboratory data. However, the vast majority of disease burden due to malaria was a result of YLL and not YERF. Since adjustment for underreporting would only affect the YERF calculation, and YERF contributed very little to the overall disease burden, it is unlikely that adjustment for underreporting would have significantly changed the estimate of disease burden.

4.9.4. TYPHOID/PARATYPHOID FEVER

Typhoid/paratyphoid fever are caused by *Salmonella typhi* and *Salmonella paratyphi*, respectively; these are bacteria spread from human to human via the fecal-oral route (in contrast to other foodborne *Salmonella* infections; see section 4.5.3 on intestinal infections). Almost all infections are acquired during travel to developing countries, particularly in South Asia. Infection is characterized by unrelenting fever, sweating, headache and diarrhea (typhoid fever). In the absence of antibiotic treatment, bowel perforation can ensue after three to four weeks of illness. Fortunately, the case fatality ratio is less than 1% among travelers returning to industrialized countries.

Data sources and HALY calculation

Since typhoid and paratyphoid fever are reportable diseases in Ontario, we used an agent-based approach to calculate disease burden. For YLL, we used Ontario vital statistics data to determine the number of deaths due to typhoid and paratyphoid fevers. For YERF, we extracted reported cases of typhoid and paratyphoid fever from Ontario's reportable disease database (iPHIS) and treated each reported case as an acute infectious episode of typhoid/paratyphoid fever. We used epidemiologic studies to determine the duration of typhoid/paratyphoid fever.

Exhibit 4.70
Parameters for estimating the disease burden due to typhoid/paratyphoid fever

Health state	Percentage of Reported Typhoid/ Paratyphoid Fever Cases per Year that Progress to Health State	Duration	Severity Weight
Acute infectious episode of typhoid/paratyphoid fever	100	4 weeks[175]	0.052

Estimated burden

We estimated annual averages of 0 deaths and 133 incident cases attributable to typhoid/paratyphoid fever. Since there were no deaths due to typhoid/paratyphoid fever, the entire disease burden was from YERF. Disease burden was relatively equal between males and females and affected mostly individuals from one to 44 years of age.

Limitations

These estimates for the burden of typhoid/paratyphoid fever are limited by the sources of uncertainty arising from symptomatic cases not seeking medical attention or from physicians failing to consider a diagnosis of typhoid/paratyphoid fever or failing to collect specimens for laboratory testing among symptomatic cases presenting with fever. There are also data quality issues associated with the reportable disease and laboratory data.

CHAPTER 5

Strengths and Limitations

5.1 STRENGTHS

This study had a number of strengths that distinguish ONBOIDS from previous burden of disease studies.

Use of the pathogen-based approach

One advance from previous burden of disease studies is that we used the pathogen-based approach to a greater extent than ever before. While we also provided estimates of the burden of selected non-specific syndromes (e.g., pneumonia, septicaemia, acute otitis media; see Appendix C) to facilitate comparisons with other studies and to assess the potential impact of non-pathogen-specific interventions, the pathogen-based approach allows for the potential impact of interventions that target specific pathogens, such as vaccines.

Comprehensiveness of infectious diseases included

We estimated the burden of 51 distinct infectious agents. To our knowledge, this is the greatest number of pathogens ever included in a burden of disease study. In comparison, a pilot study estimating the burden of infectious diseases in Europe included only seven infectious agents.[3] One of the benefits of the methodology used is that it allows for other infectious diseases to be added to the analyses in the future.

Inclusion of broader range of health states/sequelae of infectious diseases

We included a greater range of health states representing longer-term sequelae of infectious diseases (e.g., HPV-related cancers, sequelae of bacterial meningitis). This allowed us to better elucidate the true burden of these diseases.

Use of linkable health care utilization data

Although the use of health care utilization data to supplement reportable disease data in burden of disease studies is not novel, we are not aware of any previous studies that were able to link individuals across datasets. In ONBOIDS, we were able to use linkable health care utilization data to define episodes of care across health care settings for each case of a certain infectious diseases (e.g., a case of pneumonia being treated in both outpatient and inpatient settings), so we were not only assessing health care use. This approach would be further strengthened with the anticipated capacity to link health care utilization data with cause-specific mortality data in Ontario, and eventually with more province-wide microbiology data.

Expertise of investigative team

This report benefited from the involvement of numerous experts who contributed wide-ranging content and methodological expertise. The investigative team brought tremendous clinical and public health expertise that covered all the infectious diseases included in this study.

5.2 LIMITATIONS

Assumptions need to be made in order to estimate disease burden. The limitations of this study are presented in three sections: those that affected the overall study (i.e., both YLL and YERF estimates); those specific to YLL estimates; and those specific to YERF estimates. Limitations related to data sources used in this study are presented within each of these sections.

A. OVERALL LIMITATIONS IMPACTING BOTH YLL AND YERF ESTIMATES

Static nature of burden of disease methodology

One important assumption common across all studies based on the Global Burden of Disease methodology is that the natural history of a disease and the relationship between incident cases and eventual mortality remain constant over time. This assumption is particularly important for infectious diseases due to their dynamic nature.

The burden of infectious diseases may be affected by: 1) long-term changes (e.g., demographic trends, improved public sanitation) and 2) abrupt changes, such as the development of new preventive measures (e.g., vaccines) or therapies (e.g., antibiotics/antivirals), the occurrence of localized outbreaks, epidemics or pandemics (e.g., influenza) and the emergence of new pathogens or antibiotic resistance among current pathogens. ONBOIDS is limited to a static assessment of the burden of infectious diseases by: using the available Ontario data and epidemiologic studies that are necessarily restricted to a certain point in time (may not always reflect the current situation in Ontario), and not making projections to account for changes in population demographics, trends in disease incidence and mortality, and the full impact of real and potential outbreaks. In order to properly capture these aspects, dynamic mathematical modeling would be required, but this was out of scope of this project. Further studies are required to define how the dynamic nature of infectious diseases can be captured in

a burden of disease study. However, the current ONBOIDS analysis can provide the framework for future updates and reassessment of the provincial burden of infectious diseases.

Data quality and availability

Another major limitation of burden of disease studies is that the estimates depend greatly on the quality of the available data. In an ideal world, valid, timely and locally-derived data would be available for all required parameters (disease incidence, health state distribution and duration, severity weights, and mortality; all disaggregated by age and sex). In practice, however, burden of disease studies have to use existing data. For ONBOIDS, some data were not timely (e.g., vital statistics), others were not entirely complete (e.g., case counts of certain reportable diseases) or optimally validated (e.g., numbers generated through expert opinion), and a lot of parameters for health state/etiologic agent distribution and disease duration were determined from epidemiologic studies that may not necessarily apply to Ontario.

Herein lies one of the major findings of this investigation: improvements in the quality, depth and timeliness of Ontario vital statistics and infectious disease reporting data would permit improved assessments of disease burden. Secondary analysis of administrative data is always likely to have limitations in comparison with primary public health data. We attempted to ensure face validity of our results through review by numerous local experts, but the reader needs to be aware that these estimates often represent merely informed opinion. Finally, data are not available in Ontario to allow us to examine some important issues such as those related to equity and ethnicity; nor did we attempt to describe intra-provincial variation.

Focus limited to health burden

By focusing on HALYs we considered only premature mortality and year-equivalents of reduced functioning from living with the disease, and we did not take into account other important burdens. For example, there are tremendous direct (health care costs) and indirect economic burdens (work/school absenteeism, industry costs) associated both with infectious diseases and efforts to prevent infectious diseases (e.g., vaccinations, screening for STIs). Other burdens extend to those not directly infected by these pathogens, such as the psychosocial impact of life during an outbreak; fear related to the transmissibility of certain infectious diseases and the erosion of public trust do not get captured in burden of disease studies. In ONBOIDS we were unable to take into account the societal perspective or community burden, which certainly deserves further study.

The impacts of co-morbid infections and other co-morbidities were not considered

We did not examine the impact of co-morbid infections, particularly the interaction between HIV and a variety of other infections including HBV, HCV and tuberculosis. The issue of comorbidity is likely of greater consequence for chronic diseases, where multiple conditions may co-exist for long periods of time (e.g., diabetes and depression), whereas most infections or sequelae of infectious diseases are relatively short-lived, and therefore the issue of comorbid infections should have a less significant impact relative to primary infections. However, as a consequence of not considering comorbid infections, we may have overestimated or underestimated true disease burden. Co-infection with more than one infectious agent can impact both morbidity and mortality. Not accounting for other comorbidities may have led to overestimating the disease burden if individuals with comorbidities are also those who suffer from infectious diseases, because people with chronic conditions generally have shorter life expectancies than the general population.

Generalizeability of etiologic agent distributions

Use of the syndrome-based approach for redistributing events for which the etiologic agents are often not identified requires knowledge of the distribution of the etiologic agents that cause those events. Often, we were able to identify this distribution for non-fatal cases but not for fatal cases. We made the simplifying assumptions that the distributions do not vary by age or sex, and the distribution for fatal cases was similar to that for non-fatal cases. These assumptions are likely to be invalid for many diseases, and may have led to over- or underestimates of the true burden of certain agents relative to others. For example, *S. aureus* septicaemia tends to have a worse outcome than septicaemia caused by other gram-positive bacteria,[176] and

S. pneumoniae meningitis has a worse prognosis than that caused by *N. meningitidis*.[35] Furthermore, the distributions obtained from prior epidemiologic studies may not be representative of the distribution in Ontario at the present time, especially if a preventive program has been initiated. We were also often unable to distinguish between infectious diseases acquired in the community from those acquired in health care settings. This is very important because the spectrum of pathogens is very different among patients with infectious syndromes acquired in these settings, and the interventions differ as well. Finally, these distributions are inherently susceptible to bias because the yields of microbiologic testing frequently vary by agent and syndrome.

Validity of disease codes

All of the YLL estimates and most of the YERF estimates depended on disease codes defined by the International Classification of Diseases (ICD). These codes are assigned to deaths or hospitalizations by trained abstractors, and by physicians for the purposes of billing the Ontario Health Insurance Plan (for office visits), but their accuracy for infectious diseases is, for the most part, uncertain. The validity of the hospitalization database was recently tested via abstraction of 14,500 charts from 18 Ontario hospitals.[179] Procedure codes matched exactly in 88% of cases, of which the stem of the procedure code (which assembles closely related procedures) matched in 94%. Most responsible diagnoses matched exactly in 74% of cases, and in category of disease in 80%. The physician billing database has been less extensively validated. Other burden of disease studies have raised the concern of "junk codes" that represent ill-defined conditions (e.g., septicaemia).[1] We addressed this in ONBOIDS through our syndrome-based approach to estimate disease burdens of various infectious agents.

Differential inclusion of morbidity and mortality from other ICD chapters

Our estimates of pathogen-attributable burden may be biased because we included attributable morbidity and mortality for certain non-traditional infectious causes (e.g., anogenital and oropharyngeal cancers for HPV), but not for other well-established links between infectious and chronic diseases, such as cardiovascular events precipitated by influenza infections.

Exclusion of certain important infectious agents, syndromes and health states

Due largely to lack of readily available data (i.e., disease is not reportable and is difficult to assess using health administrative data), as well as the timescale of the project, we did not include certain important infectious diseases (e.g., *Helicobacter pylori*, non-tuberculosis mycobacteria, norovirus, rotavirus, Epstein-Barr virus and Lyme disease), syndromes (e.g., surgical site infections) and health states (e.g., amputation as a consequence of an infection). However, our methodology provides a useful framework for the addition of these pathogens, syndromes and health states in future analyses. We also did not directly assess the proportion of burden related to antibiotic resistance and health care-acquired infections, both of which are important contributors to the burden of infectious diseases.

Use of different time frames for the data sources

As outlined in the Chapter 2, mortality data were from 2003–2005, whereas the reportable disease, health care utilization and cancer registry data were from 2005–2007. This was necessary because the availability of the data varied by source. We thought it was more important to use the most recently available data rather than to ensure that the time periods were the same for all the data sources.

Sensitivity of the time frame studied

Estimates of the incidence of several disease pathogens were influenced by the time frame chosen for analysis. There are several diseases which generated outbreaks in Ontario either before data collection began (e.g., *E. coli* O157:H7) or after the data collection ended (e.g., *Listeria*). Their burden would have been significantly higher had another time frame been used. Moreover, several of these diseases are undergoing or may undergo significant shifts in disease incidence due to recent or ongoing preventive measures (e.g., HPV vaccination campaign), environmental patterns (e.g., West Nile virus), or demographic trends (e.g., herpes zoster). The results here may be limited in the future for interpretation of disease burden.

Arbitrary assignment to disease groups

The results by disease groups should be interpreted with caution because the list of infectious agents included in ONBOIDS could be divided many different ways. Some infectious agents could be considered under more than one disease grouping (e.g., *S. pneumoniae* was included in the Common Bacterial Infections group and hepatitis B was included with viral hepatitis, but both could have been included in the Vaccine-Preventable Diseases group). Similarly, many of the burdensome intestinal infections are caused by bacterial pathogens, and so could have reasonably been included under the Common Bacterial Infections group.

B. LIMITATIONS SPECIFIC TO YLL ESTIMATES

Mortality data quality and availability

Estimating YLL in most burden of disease studies relies on the use of vital statistics data, and in Ontario only a single underlying cause of death was available for this study. Consequently, many deaths are attributed to non-infectious causes even if some of those deaths may have been precipitated or hastened by an infectious agent. This may occur due to failure to consider an infectious etiology, incomplete investigation for diagnosing infectious diseases or misattribution of the cause of death. Although it is fair in some cases to attribute the death to the underlying illness (e.g., cancer), because infections often hasten death, we could be missing substantial YLL in the population. Access to more information than just the underlying cause of death would permit more detailed analyses to be performed; multi-causal models may be superior.[178] Another problem specific to Ontario data is the lack of timeliness of the cause-specific mortality data. As of summer 2009 when the mortality data were compiled, the most recently available data were from 2005. Fortunately, the availability of more timely, detailed and linkable data is anticipated in the near future.

Use of Ontario life expectancy

Although it has been recommended that national burden of disease studies use the standard life table for computing YLL in order to facilitate international comparisons, it was a deliberate decision by the ONBOIDS Advisory Committee to use the Ontario life table to reflect the local burden. We conducted a sensitivity analysis using DALYs that incorporates the standard GBD life expectancy (Appendix B). Despite the methodological differences, it was reassuring to find that the results were relatively similar.

C. LIMITATIONS SPECIFIC TO YERF ESTIMATES

Burden of undiagnosed/ underreported cases

Our estimates generally do not include cases that had symptoms but did not seek medical attention and/or were not diagnosed and reported, although we attempted to adjust for underreporting and underdiagnosis when possible. While this limitation is unlikely to have a major impact for uncommon diseases that cause severe illness, the impact for common diseases that cause minor illnesses may be more substantial (e.g., viral upper respiratory tract infections, gastroenteritis). This limitation would also affect diseases where physicians fail to consider the diagnosis, even if the burden may be substantial (e.g., pertussis). Missing asymptomatic cases is acceptable because they do not contribute YERFs, since the severity weight is or approximates zero. Unfortunately, we were able to adjust for underreporting for only a small number of diseases.

Disease incidence vs. prevalence

We assumed that reported cases of reportable diseases and cases defined by health care interactions represented incident cases. Most infectious diseases are of short duration, so most instances of reportable diseases and health care encounters represent incident cases; however, it is possible that some cases may be prevalent rather than incident cases. For the subset of infectious diseases with chronic courses (e.g., HIV, HCV, HBV), we used modeling studies to obtain estimates of incidence; for HPV infection we considered the full spectrum of disease outcomes (aside from recurrent respiratory papillomatosis), including cancer outcomes. Focusing on incident cases of blood-borne viruses underestimates the impact of prevalent cases differentially in some groups, such as immigrants.

Health care utilization data quality

Health care utilization data in Ontario are collected primarily for the purposes of administering the health care system, and are used secondarily for research purposes. Therefore, the validity (i.e., sensitivity and specificity) of diagnostic (ICD and OHIP) codes for ascertaining disease, especially for

many infectious diseases, is uncertain. For example, sometimes a diagnostic code for a certain disease might be used for a physician billing claim for a visit where a physician suspects and/or is testing for the presence of a disease, but the disease may not actually be present. Additionally, the codes are not comprehensive, with some diseases lacking codes.

Another limitation is that some infections may lead to multiple health care encounters (sometimes across multiple settings). We attempted to minimize the impact of double-counting repeat encounters by linking individuals across datasets and defining episodes of care; however, if different diagnoses were coded for the different encounters that actually comprised the same illness, then these instances would be counted under each condition separately (e.g., diagnosis of acute bronchitis in physician office and then a subsequent diagnosis of pneumonia for the same instance of a lower respiratory tract illness).

For the hospitalization data, we counted all diagnoses recorded for each admission; while multiple infections may occur during the same hospitalization, we were unable to determine whether the infections occurred concomitantly or sequentially. Multiple codes were also considered for the emergency department data, although it is unlikely that multiple infections occur sequentially in that setting. Counting multiple infections separately—that actually occurred concurrently—may lead to overestimating the burden (e.g., a case of pneumonia with septicaemia is likely to account for less burden than temporally separate cases of pneumonia and septicaemia in the same individual).

For the physician claims data, only a single diagnostic code is associated with each visit; this may lead to underestimating the incidence of infectious diseases if physicians submit a claim with a patient's pre-existing chronic diseases instead of an acute illness.

Reportable disease data quality and availability

Cases of reportable diseases recorded in Ontario's iPHIS must adhere to established case definitions; however, if cases definitions are too specific (e.g., to meet the definition of a "confirmed case"), some cases of true disease may be missed. The sensitivity and specificity of the case definitions used in iPHIS have not been fully assessed. Other limitations include: the possibility of duplicates; the symptom onset date may not be available so the date recorded in iPHIS may be the specimen collection date, the lab test date or the reported date; and missing data. Lastly, due to the lengthy data cleaning process, timeliness of the data may be a concern.

Laboratory data availability

Laboratory confirmation of infectious agents is generally viewed as being the gold standard for making diagnoses of infections. However, laboratory data were not directly used for ONBOIDS for a number of reasons. First, many infections are diagnosed on clinical grounds (e.g., chickenpox) and no laboratory confirmation is sought. Laboratory confirmation is more frequently performed for more serious infections, such as those present in normally sterile sites (e.g., blood, cerebrospinal fluid), therefore laboratory data will underestimate the burden of less severe infections. Second, microbiological testing is conducted across a range of laboratories (i.e., public health, hospital, and commercial laboratories). Laboratory data are not readily available from all providers of laboratory services. Although some data from Ontario's public health laboratory system are currently available, they are generally not comprehensive because the same tests may be conducted by the other types of laboratories. For diseases for which only public health laboratories perform testing (e.g., parasitic infection), the data were not easy to extract and/or the reportable disease data were felt to be equivalent or more complete. However, laboratory data were indirectly incorporated in this report, as the estimation of the burden of some diseases (e.g., HIV) relied on laboratory data for generating the incidence estimates through modeling techniques. In the future, the Ontario Laboratory Information System may permit improved capture of laboratory data of public health importance.

Use of fixed disease duration estimates and severity weights

Due to limitations in data availability, we assumed that the durations of syndromes (e.g., septicaemia) and the severity weights did not vary by age, sex or agent (when using the syndrome-based approach for estimating disease burden). The validity of these assumptions is uncertain, and for some pathogen-syndrome combinations it is known that this assumption is incorrect.

Reliance on epidemiologic studies and expert opinion

Many of the parameters used in this study are not based on empirical Ontario data, which would have been more ideal than relying on: 1) epidemiologic studies that may not be representative of present-day Ontario; and 2) expert opinion, which may be susceptible to referral/spectrum bias. As these epidemiologic studies may or may not have been conducted within Ontario or even Canada, their generalizability to the Ontario population may be limited. This may be especially true if the studies were carried out in countries with different health care systems (e.g., the United States).

Differential burden in population subgroups

We were unable to take into account the differential burden that would be expected for certain population subgroups, such as more severe infections among people with impaired immune function or different infectious disease risks among new immigrants to Ontario. Therefore, we may have underestimated the burden of diseases that commonly occur among such subpopulations.

Conclusions and Recommendations

The Ontario Burden of Infectious Disease Study sought to estimate the burden of a wide range of infectious diseases in order to determine the relative contributions of various pathogens and inform priority setting, planning and decision-making in this area.

We adapted the Global Burden of Disease Study and the Population Health Impact of Disease in Canada methodologies and used a range of local data sources and epidemiologic studies to estimate, as comprehensively as possible, the disease burden associated with 51 distinct infectious pathogens. To our knowledge, this represents the most thorough examination of the burden of infectious diseases to date.

Some of the major findings included the following:

- Each year in Ontario, there are over seven million infectious disease episodes and nearly 4,900 deaths from infectious diseases.
- Infectious diseases accounted for 82,881 HALYs, comprising 68,213 YLL and 14,668 YERF; more than 80% of the disease burden associated with infectious diseases is from premature mortality rather than from disease-associated morbidity.
- The 10 most burdensome infectious agents are hepatitis C virus (HCV), *Streptococcus pneumoniae,* human papillomavirus (HPV), hepatitis B virus (HBV), *Escherichia coli,* human immunodeficiency virus (HIV/AIDS), *Staphylococcus aureus,* influenza, *Clostridium difficile* and rhinovirus; nearly 50% of the total burden of infectious diseases could be attributed to the top five pathogens.
- Among selected infectious syndromes, the five most burdensome are pneumonia, septicaemia, urinary tract infections, acute bronchitis and endocarditis.
- There is a dramatic range in the severity of infections, from the common cold to terminal AIDS; and duration of illness, from days (e.g., for cystitis and upper respiratory tract infections) to decades (e.g., for HIV and the sequelae of bacterial meningitis).
- A large proportion of the burden can be attributed to a small number of pathogens and syndromes for which highly effective targeted interventions (e.g., pneumococcal, HBV and HPV vaccines) and non-specific interventions (e.g., hand washing, male and female condoms) already exist, so the future burden of some of these infectious agents and syndromes may be dramatically reduced with greater uptake of available interventions.
- The mortality and morbidity due to most illnesses that can be prevented by childhood vaccination (e.g., measles, mumps, rubella, tetanus, polio and diphtheria) have been largely eliminated as a result of the success of routine childhood vaccination programs. These remain priorities to ensure that control is sustained.
- A significant burden associated with infections is caused by pathogens that constitute the human body's normal microbiological flora (e.g., *E. coli, S. aureus*). These infections often take place in health care settings; addressing this burden will require interventions that minimize transmission of these pathogens to normally sterile body sites, and emphasize the ongoing need to strengthen infection prevention programs in health care settings.
- Although the overall burden was similar between males and females, marked differences in sex-specific burden were noted for certain pathogens (HCV, HBV, HPV and HIV/AIDS) and syndromes (e.g., urinary tract infections).
- The burden of infectious diseases often correlates poorly with public perception, media attention and resource allocation; many of the pathogens ranked among the top 20 receive little recognition as significant contributors to disease burden in the population.
- The total burden of infectious diseases was equivalent to roughly 25% of the burden of all cancers.
- The ranking of infectious diseases was similar to that reported in a European pilot study that assessed the burden of only seven pathogens, and the magnitude of the burden was comparable to a previous Australian study for some infectious diseases (e.g., HIV/AIDS, chlamydia) but not others (e.g., HCV, tuberculosis). This provides some validation of our methods.

These results provide a crude ordering of infectious diseases that can be used to guide planning and policy related to public health and clinical services, as well as future research across the spectrum from basic sciences to clinical services to epidemiology and population health. Although the limitations related to the data sources and parameters required in generating these estimates precludes a greater level of precision and certainty, these results provide a reasonably robust sense of relative importance of most of the infectious diseases studied (i.e., a pathogen is in the first vs. second decile). Less important than the precise position on the list is the fact that the top 10 or 20 causes capture such a large proportion of the total burden, and that some high profile infections do not appear at all. Such information is very useful for priority setting.

Future planning, decision-making, policy development and research would benefit tremendously from improvements in data availability and quality. A top priority should be to improve the data infrastructure required for surveillance, high-quality research and program evaluation by expanding on linking data sources already in existence. With Ontario's relatively large population size (over 13 million representing approximately 40% of the Canadian population) and the pre-existence of numerous population-based data sources, realizing the linkage of individual-level data spanning laboratory, public health surveillance, health care utilization and mortality datasets would lead to an extremely rich resource for future high-quality research and robust public health action in infectious diseases. This could be attained with relatively minimal investment of resources. Efforts are also required to validate and improve the quality of existing data sources. With these enhancements to the data infrastructure in Ontario, future burden of disease studies will be able to take advantage of more timely and locally-relevant estimates of disease incidence, mortality and health state distribution. Initiatives such as the Ontario Laboratory Information System, Panorama (a new reportable disease and immunization information system) and the availability of linkable cause-specific mortality data are hoped to improve the availability of information in the future.

Topics for future surveillance and/or research studies could include the following:

- The burden of important pathogens that were not included in this report (e.g., *H. pylori,* norovirus, rotavirus, non-tuberculosis mycobacteria, Epstein-Barr virus, Lyme disease).
- The burden of infectious diseases accounting for comorbid conditions (infectious and otherwise) and a greater range of health states/conditions (e.g., cardiac mortality for influenza).
- The change in burden of infectious disease over time with respect to preventive efforts, outbreaks, environmental changes (e.g., West Nile virus) or changes in population level risk factors (e.g., safe-sex practices, intravenous drug use).
- The burden of infectious disease that is attributable to different places of acquisition such as health care-associated infections or specific geographic locations in Ontario.
- The burden averted through preventive efforts such as immunization programs, screening programs or antibiotic prophylaxis.
- The burden attributable to risk factors relevant to infectious diseases (e.g., unsafe sexual practices, poor hand hygiene).
- The relationship between infectious diseases and socio-demographic factors such as age, ethnicity and socio-economic status.
- The distribution of the burden of disease in different groups within Ontario (e.g., new immigrants, the homeless).
- The economic burden of infectious diseases and outbreaks (i.e., direct and indirect costs related to their prevention and management).
- The societal-level impacts of infectious disease outbreaks (e.g., macroeconomic, psychological).
- Refining the methodology of estimating the burden of infectious disease.

In addition to future research, we recommend action in the following areas:

- Enacting policies and enhancing knowledge exchange and dissemination to further increase the uptake of existing evidence-based interventions (e.g., pneumococcal, hepatitis B, influenza and HPV vaccines, hand hygiene, antibiotic stewardship, needle exchange programs, education to encourage safe sexual behaviours, injection drug harm reduction programs) among public health agencies, clinicians, patients and the public.
- Continuing and increasing investments for the development of new interventions targeting infectious diseases (e.g., new vaccines, new antimicrobial agents).

- Screening among immigrants for a broader range of infectious diseases than those currently required under federal regulations (i.e., HIV/AIDS, syphilis, tuberculosis). The results of this report indicate that hepatitis B and C are among the 10 most burdensome infectious diseases in Ontario. Many incident infections afflict immigrants from certain parts of the world and occur prior to immigration to Canada. Efforts to identify individuals with hepatitis B and C prior to entry, and to support them and their contacts after arrival, would facilitate prevention of a substantial portion of the burden of viral hepatitis.

The estimated burden of a disease is only one of a multitude of considerations for setting priorities for appropriate future action. A critical evaluation of the effectiveness of available interventions is another important component that will influence priority setting, and economic, political and ethical considerations need to be incorporated as well.

Efforts such as ONBOIDS serve to inform decision-making, identify areas of future research and action, and highlight gaps in data availability and quality. We hope that planners, decision-makers, practitioners and researchers will use these findings in their efforts to improve the health of Ontario's population.

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Appendix A

Detailed Description of the Development of the Severity Weights Using the CLAMES Methodology

Details of the **CLA**ssification and **ME**asurement **S**ystem of Function Health (CLAMES) methodology have been described previously.[8] In brief, investigators at Statistics Canada adapted and combined the Health Utilities Index Mark III (HUI3),[179] the Medical Outcomes Study Short-Form 36 (SF-36),[180] and the European Quality of Life Five Dimensions Index Plus (EQ-5D),[181] to create a new instrument (CLAMES) containing 11 health status attributes with the theoretical capacity to describe 10,240,000 possible health states. A subset of 238 health states was selected in order to develop a scoring function or algorithm. A total of 14 lay panels consisting of 8–11 participants each were assembled for preference measurement exercises in nine communities across Canada. The investigators used the standard gamble (SG) technique* to elicit participants' preferences for sets of health states that were blinded to minimize participant biases.[182] The investigators generated the scoring function by fitting these preferences scores with a log-linear model.

Previous Canadian studies have used the CLAMES approach to develop preferences scores for health states related to cancer and diabetes.[5]

Due to potential differences in contexts and included health states the ONBOIDS Advisory Committee felt that developing a locally relevant set of severity weights using CLAMES was preferable to combining disability weights from various prior studies.

* In the standard gamble technique, preferences for a given health state are assessed in terms of participants' willingness to undergo a specific treatment, which has a probability of either restoring them to full health or causing death.

This new set of severity weights for the health states considered in ONBOIDS was generated by a severity weights subcommittee. The subcommittee comprised two physicians with expertise in both public health and primary care, one infectious diseases physician, one general internist (who subsequently sub-specialized in infectious diseases), a member of the original CLAMES development team from Statistics Canada and the ONBOIDS project manager/epidemiologist.

After undergoing a training session to review the CLAMES methodology, the subcommittee developed new classifications for the majority of health states. For each health state, the subcommittee assigned a level for each attribute based on consensus. Attribute levels generated by the subcommittee were compared with examples from other diseases to achieve consistency. Severity weights for some health states related to infectious diseases had been previously developed by Statistics Canada, and these were used for ONBOIDS after review and confirmation of appropriateness. The overall set of severity weights (Exhibit A.1) was reviewed by the broader ONBOIDS team as a crude check of face validity.

Exhibit A.1

List of severity weights (SW) and Classification and Measurement System of Function Health (CLAMES) attributes for the health states used in ONBOIDS, in descending order of severity

		CLAMES Attributes										
Health State	**SW**	**PD**	**PF**	**EM**	**FA**	**TH**	**SR**	**AN**	**SP**	**HE**	**VI**	**HF**
Terminal care phase for cancer (last month of life)	**0.821**	4	4	4	4	4	4	3	1	1	1	4
AIDS (terminal)	**0.801**	4	4	4	4	2	4	3	1	1	1	1
Necrotizing fasciitis	**0.729**	4	4	1	4	2	3	4	1	1	1	2
Tetanus	**0.724**	3	4	4	4	1	4	3	3	1	1	4
Neonatal herpes with long-term sequelae	**0.652**	4	4	1	4	4	3	2	1	1	1	1
Septicaemia	**0.652**	4	4	1	4	4	3	2	1	1	1	1
Bacterial meningitis	**0.652**	4	4	1	4	4	3	2	1	1	1	1
Candidiasis (invasive)	**0.652**	4	4	1	4	4	3	2	1	1	1	1
Aspergillosis (invasive non-pulmonary)	**0.652**	4	4	1	4	4	3	2	1	1	1	1
Decompensated cirrhosis	**0.628**	4	3	4	4	3	2	2	1	1	1	1
Palliative care phase for cancer (last five months before terminal care phase)	**0.516**	3	3	4	3	2	4	3	1	1	1	3
Encephalitis	**0.502**	3	4	1	3	4	3	1	3	1	1	1
Ectopic pregnancy	**0.448**	4	3	3	1	1	1	3	1	1	1	1
Aspergillosis (invasive pulmonary)	**0.398**	4	2	1	4	1	1	3	1	1	1	1
Hepatocellular cancer	**0.357**	3	2	3	3	1	2	4	1	1	1	1
Dengue fever	**0.348**	4	2	1	2	1	1	1	1	1	1	1
Varicella with complications	**0.286**	1	3	1	1	3	4	1	1	1	3	5
Surgery (post operative, in patient)	**0.268**	2	3	3	3	1	3	3	1	1	1	1
End stage renal disease (dialysis)	**0.260**	3	2	3	3	1	3	3	1	1	1	1
Receiving chemotherapy (mild toxicity)	**0.250**	2	2	3	3	2	3	3	1	1	1	1
AIDS	**0.247**	2	2	3	3	2	3	2	1	1	1	1

Exhibit A.1 (CONTINUED)
List of severity weights (SW) and Classification and Measurement System of Function Health (CLAMES) attributes for the health states used in ONBOIDS, in descending order of severity

		CLAMES Attributes										
Health State	**SW**	**PD**	**PF**	**EM**	**FA**	**TH**	**SR**	**AN**	**SP**	**HE**	**VI**	**HF**
West Nile virus Neurological Manifestations (WNNM) (acute)	**0.239**	3	3	1	3	3	3	3	2	1	1	2
Receiving radiotherapy (curative)	**0.219**	3	2	3	3	1	2	3	1	1	1	1
Cancer diagnosis (poor prognosis)	**0.191**	2	2	3	2	1	3	3	1	1	1	1
Tuberculosis (TB): pulmonary infection (treated, in isolation)	**0.175**	3	2	1	2	1	4	2	1	1	1	1
Endocarditis (acute)	**0.174**	3	3	1	3	1	1	3	1	1	1	1
Malaria: *P. falciparum* (severe)	**0.174**	3	3	1	4	1	1	3	1	1	1	1
Haemolytic uraemic syndrome	**0.171**	3	3	1	3	1	2	2	1	1	1	1
Measles	**0.157**	3	3	1	3	1	2	1	1	1	1	1
Ophthalmia neonatorum	**0.147**	1	2	1	1	1	1	1	1	1	4	1
Cancer diagnosis (fairly good prognosis)	**0.147**	2	2	3	2	1	2	3	1	1	1	1
Congenital syphilis	**0.139**	2	3	1	1	2	1	1	1	2	1	1
Hepatitis A: prolonged episode	**0.136**	3	2	1	3	1	2	2	1	1	1	1
Pneumonia	**0.136**	3	2	1	3	1	1	2	1	1	1	1
Neonatal pneumonia	**0.136**	3	2	1	3	1	1	2	1	1	1	1
Pneumocystosis	**0.136**	3	2	1	3	1	1	2	1	1	1	1
Aspergillosis (non-invasive)	**0.136**	3	2	1	3	1	1	2	1	1	1	1
Blastomycosis (pulmonary)	**0.136**	3	2	1	3	1	1	2	1	1	1	1
Blastomycosis (disseminated)	**0.136**	3	2	1	3	1	1	2	1	1	1	1
Histoplasmosis	**0.136**	3	2	1	3	1	1	2	1	1	1	1
Guillain-Barré syndrome	**0.132**	3	3	1	2	1	2	2	1	1	1	2
Enterocolitis	**0.123**	3	3	1	2	1	2	2	1	1	1	1
Hepatitis B: acute symptomatic episode	**0.121**	3	2	1	3	1	2	1	1	1	1	1

Exhibit A.1 (CONTINUED)
List of severity weights (SW) and Classification and Measurement System of Function Health (CLAMES) attributes for the health states used in ONBOIDS, in descending order of severity

		CLAMES Attributes										
Health State	**SW**	**PD**	**PF**	**EM**	**FA**	**TH**	**SR**	**AN**	**SP**	**HE**	**VI**	**HF**
Hepatitis C: acute symptomatic episode	**0.121**	3	2	1	3	1	2	1	1	1	1	1
WNNM (long-term sequelae)	**0.111**	3	2	1	1	2	2	2	2	1	1	2
Infertility	**0.109**	1	1	3	1	1	2	3	1	1	1	1
Cancer diagnosis (very good prognosis)	**0.109**	1	1	3	1	1	2	3	1	1	1	1
Septic arthritis	**0.108**	3	3	1	2	1	1	1	1	1	1	1
Poliomyelitis	**0.093**	2	2	1	3	1	2	1	1	1	1	1
Bronchitis (acute)	**0.086**	3	2	1	1	1	1	2	1	1	1	1
Bronchiolitis	**0.086**	3	2	1	1	1	1	2	1	1	1	1
Pelvic inflammatory disease	**0.086**	3	2	1	2	1	2	2	1	1	1	1
Gastroenteritis (severe)	**0.086**	3	2	1	2	1	2	2	1	1	1	1
Mesenteric adenitis	**0.086**	3	2	1	2	1	2	2	1	1	1	1
Acute intestinal infection with bloody diarrhea	**0.086**	3	2	1	2	1	2	2	1	1	1	1
TB: extra-pulmonary infection, non-lymph node	**0.086**	3	2	1	2	1	2	2	1	1	1	1
Neurosyphilis	**0.074**	2	2	1	2	3	2	2	2	1	1	1
Deafness	**0.071**	1	1	1	1	1	2	1	2	3	1	1
Hepatitis A: uncomplicated episode	**0.070**	3	2	1	2	1	2	1	1	1	1	1
Pyelonephritis	**0.070**	3	2	1	2	1	1	1	1	1	1	1
Cellulitis	**0.070**	3	2	1	1	1	1	1	1	1	1	1
TB: pre-diagnosed pulmonary infection (contagious)	**0.070**	3	2	1	2	1	1	1	1	1	1	1
Primary genital herpes syndrome	**0.068**	3	1	1	1	1	2	2	1	1	1	1
Zoster with complications	**0.068**	3	1	2	1	1	1	2	1	1	1	1
Motor deficits	**0.062**	1	2	2	1	2	2	2	2	1	1	2

Exhibit A.1 (CONTINUED)
List of severity weights (SW) and Classification and Measurement System of Function Health (CLAMES) attributes for the health states used in ONBOIDS, in descending order of severity

		CLAMES Attributes										
Health State	**SW**	**PD**	**PF**	**EM**	**FA**	**TH**	**SR**	**AN**	**SP**	**HE**	**VI**	**HF**
Post liver transplant	**0.057**	2	2	1	2	1	1	2	1	1	1	1
Otitis media	**0.052**	3	1	1	2	1	1	1	1	1	1	1
Pharyngitis	**0.052**	3	1	1	2	1	1	1	1	1	1	1
Acute zoster episode (shingles)	**0.052**	3	1	1	1	1	1	1	1	1	1	1
Typhoid/paratyphoid fever	**0.052**	3	1	1	2	1	2	1	1	1	1	1
Candidiasis (semi-invasive)	**0.052**	3	1	1	1	1	1	1	1	1	1	1
Osteomyelitis	**0.041**	2	2	1	2	1	1	1	1	1	1	1
Gastroenteritis (moderate)	**0.041**	2	2	1	2	1	2	1	1	1	1	1
Post-colectomy state	**0.041**	2	2	2	1	1	2	1	1	1	1	1
Reactive arthritis	**0.041**	2	2	1	2	1	1	1	1	1	1	1
Chronic giardiasis	**0.041**	2	2	1	2	1	2	1	1	1	1	1
Acute intestinal infection with non-bloody diarrhea	**0.041**	2	2	1	2	1	2	1	1	1	1	1
Pertussis	**0.041**	2	2	1	1	1	2	1	1	1	1	1
Diphtheria	**0.041**	2	2	1	1	1	2	1	1	1	1	1
Prostatitis (acute)	**0.039**	2	1	1	1	1	2	2	1	1	1	1
Seizure disorder	**0.039**	2	1	1	2	1	2	2	1	1	1	1
Secondary syphilis	**0.039**	2	1	1	2	1	2	2	1	1	1	1
Urethritis	**0.039**	2	1	1	1	1	2	2	1	1	1	1
Cervicitis	**0.039**	2	1	1	1	1	2	2	1	1	1	1
Epididymitis/orchitis/prostatitis	**0.039**	2	1	1	1	1	2	2	1	1	1	1
Irritable bowel syndrome	**0.039**	2	1	1	1	1	2	2	1	1	1	1
Neurological complications from diphtheria	**0.039**	2	1	1	2	1	2	2	1	1	1	1
Chronic hepatitis (B and C)	**0.035**	1	2	1	2	1	2	2	1	1	1	1
HIV	**0.035**	1	2	2	2	1	2	2	1	1	1	1

Exhibit A.1 (CONTINUED)
List of severity weights (SW) and Classification and Measurement System of Function Health (CLAMES) attributes for the health states used in ONBOIDS, in descending order of severity

		CLAMES Attributes										
Health State	**SW**	**PD**	**PF**	**EM**	**FA**	**TH**	**SR**	**AN**	**SP**	**HE**	**VI**	**HF**
Cancer remission (after all forms of treatment)	**0.035**	1	2	2	2	1	2	2	1	1	1	1
Cystitis (bladder)	**0.023**	2	1	1	1	1	1	1	1	1	1	1
Upper respiratory tract infection	**0.023**	2	1	1	2	1	1	1	1	1	1	1
Conjunctivitis	**0.023**	2	1	1	1	1	1	1	1	1	1	1
Symptomatic herpes without PGHS	**0.023**	2	1	1	1	1	2	1	1	1	1	1
Recurrent genital herpes	**0.023**	2	1	1	1	1	2	1	1	1	1	1
Trichomoniasis	**0.023**	2	1	1	1	1	2	1	1	1	1	1
Gastroenteritis-mild	**0.023**	2	1	1	1	1	2	1	1	1	1	1
TB: pulmonary infection (treated, not in isolation)	**0.023**	2	1	1	1	1	2	1	1	1	1	1
TB: extra-pulmonary infection, lymph node	**0.023**	2	1	1	2	1	2	1	1	1	1	1
Acute varicella episode (chickenpox)	**0.023**	2	1	1	2	1	2	1	1	1	1	1
Mumps	**0.023**	2	1	1	2	1	2	1	1	1	1	1
Rubella	**0.023**	2	1	1	2	1	2	1	1	1	1	1
Congenital rubella syndrome	**0.023**	2	1	1	2	1	2	1	1	1	1	1
Malaria: *P.falciparum* (not severe)	**0.023**	2	1	1	2	1	1	1	1	1	1	1
Malaria: *non-P. falciparum malaria*	**0.023**	2	1	1	2	1	1	1	1	1	1	1
West Nile fever	**0.023**	2	1	1	2	1	1	1	1	1	1	1
Candidiasis (non-invasive)	**0.023**	2	1	1	1	1	1	1	1	1	1	1
Primary syphilis	**0.017**	1	1	1	1	1	2	2	1	1	1	1
HPV - anogenital warts	**0.017**	1	1	1	1	1	2	2	1	1	1	1

PD = pain or discomfort (maximum value, 4)
PF = physical functioning (maximum value, 4)
EM = emotional state (maximum value, 5)
FA = fatigue (maximum value, 4)
TH = memory and thinking (maximum value, 4)
SR = social relationships (maximum value, 5)
AN = anxiety (maximum value, 4)
SP = speech (maximum value, 4)
HE = hearing (maximum value, 4)
VI = vision (maximum value, 4)
HF = use of hands and fingers (maximum value, 5)

Appendix B

Comparison of the Burden of Infectious Diseases Using the Standard Global Burden of Disease (GBD) and Ontario Burden of Infectious Disease Study (ONBOIDS) Methodologies

As mentioned in section 2.1, the methodology used to estimate the burden of infectious diseases in this study differed from methods used to estimate disease burden in previous studies such as the GBD and Australian Burden of Disease and Injury studies. Specifically, those other studies used disability-adjusted life years (DALYs), an outcome measure that differed from ours in four important aspects (Exhibit B.1).

Exhibit B.1

Differences between health-adjusted life years (HALYs), used in the Ontario Burden of Infectious Disease Study (ONBOIDS), and disability-adjusted life years (DALYs), used in the Global Burden of Disease (GBD) study

Health State	HALYs (ONBOIDS)	DALYs (GBD)
Life expectancy table	Ontario, 2001 Life expectancy at birth: 82 years for females, 77.4 years for males)	GBD standard Life expectancy at birth: 82.5 years for females, 80 years for males
Age-weighting	Uniform age weights (i.e., no age-weighting)	Differential age-weights (more weight for working age adults)
Discounting	No discounting	Discount rate of 3%
Health state valuation	Severity weights (CLAMES instrument— see Appendix A)	Disability weights (from previous studies)

We conducted a sensitivity analysis to facilitate comparisons between our study and the infectious disease section of other burden of disease studies, as well as to evaluate the robustness of our pathogen rankings using another outcome measure. We used the standard DALY methodology (using the standard GBD life expectancy for years of life lost [YLL] calculation, applying age-weights, discounting at a rate of 3%, and using disability weights) to estimate the burden of the top 20 pathogens (accounting for approximately 75% of the burden calculated in our primary analysis). In order to conduct this analysis, we obtained the DALY template worksheets from the WHO website and inputted our incidence and mortality counts.[183] We used previously published burden of disease studies to obtain disability weights for our health states. When there was a health state in our study that was not reported in any other burden of disease study, we approximated its disability weight using the weights of other related conditions as reference points.

The overall ranking of pathogens was relatively consistent between the two methodologies (Exhibits B.1, B.2 and 3.5). For instance, the top six pathogens were the same regardless of the methodology, and nine out of the top 10 pathogens using the ONBOIDS method were also ranked in the top 10 using the GBD method (the exception was *Clostridium difficile* which fell from ninth to twelfth position and was replaced by chlamydia in the top 10).

Exhibit B.2

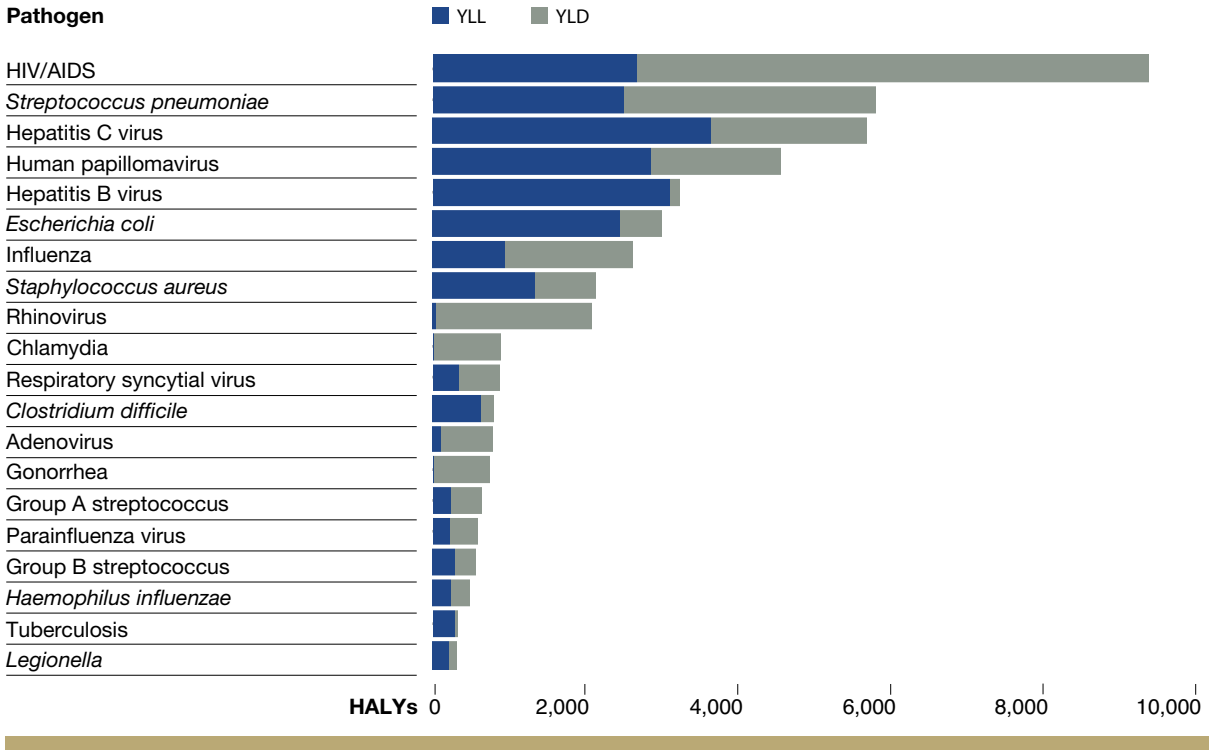
Burden of disease ranking of the top 20 pathogens using Ontario Burden of Infectious Disease Study (ONBOIDS) and Global Burden of Disease (GBD) study methodologies

Ranking		ONBOIDS Methodology				GBD Methodology		
#	Pathogen	YLL	YERF	HALYs	Pathogen	YLL	YLD	DALYs
1	Hepatitis C virus	7,729	983	8,713	HIV/AIDS	2,676	6,731	9,407
2	*Streptococcus pneumoniae*	6,475	1,601	8,076	*Streptococcus pneumoniae*	2,506	3,309	5,815
3	Human papillomavirus	6,167	1,418	7,585	Hepatitis C virus	3,657	2,042	5,699
4	Hepatitis B virus	6,698	86	6,785	Human papillomavirus	2,869	1,704	4,573
5	*Escherichia coli*	6,430	341	6,771	Hepatitis B virus	3,107	143	3,250
6	Ex HIV/AIDS	4,929	1,312	6,242	*Escherichia coli*	2,462	550	3,012
7	*Staphylococcus aureus*	3,320	400	3,720	Influenza	952	1,678	2,630
8	Influenza	2,548	1,076	3,624	*Staphylococcus aureus*	1,343	789	2,132
9	*Clostridium difficile*	1,721	107	1,828	Rhinovirus	40	2,047	2,087
10	Rhinovirus	95	1,615	1,710	Chlamydia	13	883	896
11	Respiratory syncytial virus	914	397	1,310	Respiratory syncytial virus	337	547	884
12	Parainfluenza virus	581	259	840	*Clostridium difficile*	635	169	804
13	Group B streptococcus	700	123	823	Adenovirus	110	676	786
14	Group A streptococcus	574	216	791	Gonorrhea	13	736	749
15	*Haemophilus influenzae*	628	125	754	Group A streptococcus	232	410	642
16	Tuberculosis	647	15	662	Parainfluenza virus	222	376	598
17	*Legionella*	570	40	609	Group B streptococcus	293	270	563
18	Chlamydia	28	442	470	*Haemophilus influenzae*	242	241	483
19	Adenovirus	287	150	437	Tuberculosis	287	42	329
20	Gonorrhea	27	371	398	*Legionella*	217	94	311
	Total	51,069	11,078	62,147	**Total**	22,213	23,437	45,650

YLL = years of life lost due to premature mortality; YERF = year-equivalents of reduced functioning; HALY = health-adjusted life years; YLD = years of life lived with disability; DALY = disability-adjusted life years

Exhibit B.3

Burden of disease ranking for the top 20 pathogens, based on years of life lost due to premature mortality (YLL), years of life lived with disability (YLD) and disability-adjusted life years (DALYs)



Note: See Exhibit 3.5 for a comparison of the disease burden for the top 20 pathogens based on years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs)

Despite the similarities in the top five and top 10 rankings of the two approaches, some important differences merit discussion. First and foremost, the use of age-weighting and discounting substantially diminishes the mortality component for infectious diseases that predominantly cause death in older age groups. *C. difficile* and *E. coli* are examples of pathogens for which death occurred most commonly in elderly individuals, and the application of age-weighting and discounting halved the burden attributable to those diseases. Second, disability weights tended to be higher in magnitude than the severity weights derived for ONBOIDS. This meant that pathogens associated with common conditions or long-term sequelae had increased burden. For instance, the ascension of rhinovirus in the ranking was the result of a number of common syndromes (e.g., upper respiratory tract infection, acute bronchitis) for which the disability weights were higher than the ONBOIDS severity weights, resulting in a higher estimate of YLD compared to YERF. Similarly, the HIV/AIDS health states had higher disability weights than severity weights, as did infertility for chlamydial- and gonococcal-associated pelvic inflammatory disease and the chronic carrier state of hepatitis C. These differences resulted in large increases in the morbidity components for these pathogens.

Consequently, while the ranking of the top pathogens was relatively unchanged using the summary measure, the relative contributions of the mortality and morbidity components changed substantially. Using the ONBOIDS methodology, YLL accounted for 82% of the HALYs for the top 20 pathogens, whereas the GBD approach led to YLL accounting for only 49% of DALYs for those pathogens (Exhibit B.2). Because the differences between the methodologies essentially amount to value judgments, it is not possible to definitively determine which approach is more valid, but the differences may influence the choice of interventions to address the burden of a particular disease (i.e., whether to target mortality vs. morbidity).

In summary, despite the important methodological differences between the standard GBD method and the approach used in ONBOIDS, it is reassuring that the rankings of the pathogens using the two methods are relatively similar—leading to the same general conclusions for informing policy and decision-making. Although the relative contributions of mortality and morbidity vary depending on the methodology, there is uncertainty regarding which should be considered the "gold standard."

Appendix C

Burden of Selected Syndromes

As mentioned in Chapter 2, when reportable disease data were unavailable and/or were identified as being insufficiently comprehensive (e.g., diseases where only invasive infections were reported), health care utilization data were used to estimate disease incidence.

Episodes of common syndromes (e.g., pneumonia, otitis media) were identified using physician services, emergency room and hospitalization data. Estimates from the literature were used to attribute proportions of that syndrome to specific infectious agents.

Appendix C provides a brief description of each syndrome considered in ONBOIDS, outlines the attributable fractions (i.e., proportions used for each syndrome to assign episodes/deaths to specific infectious agents) and characterizes the burden of each syndrome in Ontario.

C.1 PNEUMONIA

Pneumonia is an inflammatory condition of the lung, which can result from infection from a wide variety of organisms: bacteria, viruses, fungi or parasites. Individuals with pneumonia often have a cough producing greenish or yellow sputum and a high fever with accompanying chills. Chest pain, shortness of breath, fatigue and nausea are other common symptoms of pneumonia. Pneumonia can lead to additional complications such as respiratory and circulatory failure. Systemic antibiotics are used to treat bacterial pneumonia; there are fewer treatment options for viral pneumonia.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to pneumonia. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for pneumonia. We used epidemiologic studies to determine the percentage of pneumonia caused by various pathogens and the duration of illness that pneumonia typically causes with adequate treatment.

Exhibit C.1
Parameters for estimating the disease burden due to pneumonia

Infectious Agent	Percentage of Pneumonia Attributable to Infectious Agent	Number of Pneumonia Episodes Attributable to Infectious Agent	Number of Pneumonia Deaths Attributable to Infectious Agent
Streptococcus pneumoniae	30[39]	75,742	586
Influenza	10[110]	25,247	195
Other gram-negative bacteria	10[48]	25,247	195
Respiratory syncytial virus (RSV)	2 (10–14 years)[117] 2 (15–64 years)[110] 5 (≥65 years)[118]	18,687	95
E. coli	3.6[48]	9,089	70
H. influenzae	3[73]	7,574	59
Legionella	3[39]	7,574	59
Parainfluenza virus	3[110]	7,574	59
S. aureus	3[39]	7,574	59
Adenovirus	1.5[110]	3,787	29
Group A streptococcus	1[184]	2,525	20
Other pathogens	24.4	61,852	529

Estimated burden

We estimated annual averages of 1,954 deaths and 252,473 health care utilization episodes for pneumonia. Most of the disease burden was from YLL. Disease burden was slightly higher in females and mainly affected individuals aged 65 or older.

C.2 SEPTICAEMIA

Septicaemia is an inflammatory state characterized by the presence of pathogenic organisms in the bloodstream that can lead to sepsis. Septicaemia leads to acute inflammation throughout the entire body and is frequently associated with fever or lowered body temperature. If severe sepsis develops, septic shock can occur, as well as organ dysfunction/failure and death. Septicaemia is usually treated with intravenous fluids and antibiotics—and possibly intensive care—including medications that support blood pressure and organ perfusion.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to septicaemia. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for septicaemia. We used epidemiologic studies to determine the percentage of septicaemia caused by various pathogens and the duration of illness that septicaemia typically causes with adequate treatment.

Exhibit C.2
Parameters for estimating the disease burden due to septicemia

Infectious Agent	Percentage of Septicaemia Attributable to Infectious Agent	Number of Septicaemia Episodes Attributable to Infectious Agent	Number of Septicaemia Deaths Attributable to Infectious Agent
Other gram-positive bacteria	24.5[57]	3,817	171
E. coli	24[37]	3,723	167
Other gram-negative bacteria	22.1[37]	3,443	155
S. aureus	15.5[37]	2,415	109
S. pneumoniae	4.8[37]	748	34
Group B streptococcus	1[57, 58]	156	7
Group A streptococcus	0.6[66]	94	4
H. influenzae	0.4[72]	62	3
Other pathogens	6.2	966	50

Estimated burden

We estimated annual averages of 700 deaths and 15,578 health care utilization episodes for septicaemia. The vast majority of disease burden was from YLL. Disease burden was slightly higher in women. Approximately 50% of the disease burden affected individuals aged 65 or older. Disease burden was also high in those aged 40–64 and in children from birth to four years of age.

C.3 URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) include bladder infections (cystitis) and kidney infections (pyelonephritis). *E. coli* is the most common etiologic agent causing cystitis and pyelonephritis. Symptoms of these infections include frequent urination, pain/discomfort during urination and cloudy urine; pyelonephritis may additionally present with flank pain or fever. In most cases, cystitis is easily treated with a short course of antibiotics; pyelonephritis is treated more aggressively with a longer course of antibiotics or intravenous antibiotics and is more likely to require hospitalization.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to UTIs. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for UTIs. We used epidemiologic studies to determine the percentage of UTIs caused by various pathogens and the duration of illness that UTIs typically cause with adequate treatment.

Exhibit C.3
Parameters for estimating the disease burden due to urinary track infections

Infectious Agent	Percentage of UTIs Attributable to Infectious Agent	Number of UTI Episodes Attributable to Infectious Agent	Number of UTI Deaths Attributable to Infectious Agent
E. coli	80[49]	438,438	362
Other gram-negative bacteria	10[49]	54,805	45
Other gram-positive bacteria	3.8[77]	20,826	17
Other pathogens	6.2	33,979	28

Estimated burden

We estimated annual averages of 452 deaths and 548,047 health care utilization episodes for UTIs. Most of the disease burden was from YLL and occurred in individuals aged 65 or older. Disease burden attributable to UTIs for females was twice the burden for males.

C.4 ACUTE BRONCHITIS

Bronchitis is the inflammation of the mucous membranes of the airways (bronchi) that carry oxygen from the trachea to the lungs. Acute bronchitis typically results from infection with a viral respiratory pathogen but may also occur from a bacterial infection. Acute bronchitis is characterized by chronic cough, excessive production of sputum, sore throat, runny nose, low-grade fever and fatigue. Non-steroidal anti-inflammatory drugs, decongestants and cough suppressants may be used to treat the symptoms of acute bronchitis, but the majority of cases resolve themselves.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to acute bronchitis. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for acute bronchitis. We used epidemiologic studies to determine the percentage of acute bronchitis by various pathogens and the duration of illness that acute bronchitis typically causes with adequate treatment.

Exhibit C.4
Parameters for estimating the disease burden due to acute bronchitis

Infectious Agent	Percentage of Acute Bronchitis Attributable to Infectious Agent	Number of Acute Bronchitis Episodes Attributable to Anfectious Agent	Number of Acute Bronchitis Deaths attributable to Infectious Agent
Rhinovirus	33[42]	327,526	4
Influenza	24[42]	238,201	3
Streptococcus pneumoniae	20[42]	198,501	3
Coronavirus	6.25[42]	62,031	1
Parainfluenza	3.75[42]	37,219	1
Respiratory syncytial virus	0–64 years: 2.5[42] ≥65 years: 12[119]	45,122	1
Other pathogens	0–64 years: 10.5 ≥65 years: 1	83,914	0

Estimated burden

We estimated annual averages of 13 deaths and 992,503 health care utilization episodes for acute bronchitis. Most of the disease burden was from YERF. Disease burden was similar between males and females and across age groups.

C.5 ENDOCARDITIS

Endocarditis involves inflammation of the inner layer of the heart (endocardium)—in particular the heart valves. Certain bacteria have a capacity to adhere to clot on damaged heart valves, resulting in the growth of a nidus of infection, called a vegetation. The effector cells of the immune system cannot penetrate this vegetation, and so this infection was uniformly fatal in the pre-antibiotic era. Treatment requires prolonged intravenous antibiotics and potentially heart valve replacement. Mortality rates are still significant and complications include congestive heart failure and embolism (including stroke).

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to endocarditis. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for endocarditis. We used epidemiologic studies to determine the percentage of endocarditis by various pathogens and the duration of illness that endocarditis typically causes with successful treatment.

Exhibit C.5
Parameters for estimating the disease burden due to endocarditis

Infectious Agent	Percentage of Endocarditis Attributable to Infectious Agent	Number of Endocarditis Episodes Attributable to Infectious Agent	Number of Endocarditis Deaths Attributable to Infectious Agent
Other gram-positive bacteria	42[76]	539	74
S. aureus	26[52]	334	46
Other gram-negative bacteria	2[75]	26	4
Other pathogens	30	385	52

Estimated burden

We estimated annual averages of 175 deaths and 1,284 health care utilization episodes for endocarditis. Most of the disease burden was from YLL. Disease burden was equal among males and females and mainly affected individuals aged 40 or older.

C.6 UPPER RESPIRATORY TRACT INFECTIONS

Acute upper respiratory tract infections (URTIs) included: rhinitis (inflammation of nasal mucosa), epiglottitis (inflammation of the superior portion of the larynx), laryngitis (inflammation of the larynx) and tracheitis (inflammation of the trachea). Pharyngitis, which is often considered a URTI, was considered as a separate syndrome in this report. URTIs are typically caused by viruses, particularly rhinovirus. The common symptoms of URTIs are cough, sore throat, sneezing, runny nose and nasal congestion. Fever and fatigue are less common symptoms. There is no standard treatment for URTIs, but some medication may be taken for symptom relief. Bacterial complications of viral URTIs, such as otitis media or sinusitis, may be treated with antibiotics.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to URTIs. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for URTIs. We used epidemiologic studies to determine the percentage of URTIs by various pathogens and the duration of illness that URTIs typically cause with adequate treatment.

Exhibit C.6
Parameters for estimating the disease burden due to upper respiratory tract infections (URTIs)

Infectious Agent	Percentage of URTIs Attributable to Infectious Agent	Number of URTIs Episodes Attributable to Infectious Agent	Number of URTIs Deaths Attributable to Infectious Agent
Rhinovirus	40[114]	1,279,154	1
Coronavirus	12.5[114]	399,736	0
Influenza	10[114]	319,789	0
Respiratory syncytial virus	5[114]	159,894	0
Parainfluenza	5[114]	159,894	0
Adenovirus	2.5[114]	79,947	0
Other pathogens	25	799,472	1

Estimated burden

We estimated annual averages of two deaths and 3,197,886 health care utilization episodes for URTIs. Most of the disease burden was from YERF. Disease burden was slightly higher in females and the burden was skewed toward the younger age groups.

C.7 BACTERIAL MENINGITIS

Bacterial meningitis is the inflammation of the protective membrane surrounding the brain and spinal cord caused by a bacterial infection. The most common symptoms of bacterial meningitis are headache, neck stiffness, fever, rash, nausea and impaired level of consciousness. Bacterial meningitis can lead to long-term complications, such as hearing loss, seizure disorders and neurological/motor deficits. The treatment of bacterial meningitis is complicated and generally involves empiric antibiotic treatment (given before the causative agent is known), followed by more specific antibiotic treatment once the exact pathogen has been identified.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to bacterial meningitis. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for bacterial meningitis. We used epidemiologic studies to determine the percentage of bacterial meningitis by various pathogens, the percentage of bacterial meningitis cases that proceeded to certain sequelae (seizure disorders, motor deficits and hearing loss) and the duration of illness that bacterial meningitis typically causes with adequate treatment.

Exhibit C.7
Parameters for estimating the disease burden due to bacterial meningitis

Infectious Agent	Percentage of URTIs Attributable to Infectious Agent	Number of URTIs Episodes Attributable to Infectious Agent	Number of URTIs Deaths Attributable to Infectious Agent
Streptococcus pneumoniae	32 (0–4 years) 45 (5–14 years) 51 (≥15 years)[33, 34]	146	9
Neisseria meningitidis	25 (0–4 years) 35 (5–14 years) 37 (≥15 years)[33, 34]	108	7
Group B streptococcus	22 (0–4 years) 6 (5–14 years) 1 (15+ years)[33, 34]	24	1
E. coli	7 (0–14 years) 1 (≥15 years)[33, 34]	10	0
H. influenzae	4 (0–14 years) 2 (≥15 years)[33, 34]	9	0
Other gram-negative bacteria	3 (0–14 years) 1 (≥15 years)[33, 34]	5	0
Other pathogens	7 (0–4 years) 0 (5–14 years) 7 (≥15 years)[33, 34]	22	1

Estimated burden

We estimated annual averages of 19 deaths and 324 health care utilization episodes for bacterial meningitis. The disease burden from YLL and YERF was relatively even. Disease burden was equal between males and females and most of the disease burden occurred in children from birth to 14 years and adults aged 30–64. It is important to note that *Listeria* is an important cause of bacterial meningitis.[34] However, since the disease burden for *Listeria* was not calculated using the syndrome-based approach, it does not appear in the above table. From Exhibit 4.41, it can be seen that 16 meningitis cases per year are expected to develop from *Listeria* infection. These 16 cases would likely correspond to a large proportion of the 22 cases of meningitis we expect from "other pathogens".

C.8 CELLULITIS

Cellulitis is inflammation of the dermal and subcutaneous layers of the skin that can be caused by normal skin flora or by exogenous bacteria. Cellulitis often occurs in areas where skin breakdown (wound, catheter insertion, etc.) facilitates bacterial entry, or impaired lymphatic drainage (following surgery, radiation, venous insufficiency, etc.) prevents bacterial clearance. The infected area is often reddish in colour, warm to the touch and tender. Oral or intravenous antibiotics can be given for treatment depending on the severity of the inflammation.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to cellulitis. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for cellulitis. We used epidemiologic studies to determine the percentage of cellulitis by various pathogens and the duration of illness that cellulitis typically causes with adequate treatment.

Exhibit C.8
Parameters for estimating the disease burden due to cellulitis

Infectious Agent	Percentage of Cellulitis Attributable to Infectious Agent	Number of Cellulitis Episodes Attributable to Infectious Agent	Number of Cellulitis Deaths Attributable to Infectious Agent
S. aureus	50[54]	142,293	30
Group A streptococcus	28.5[54]	81,107	17
Group B streptococcus	2[185]	5,692	1
Other pathogens	19.5	55,494	12

Estimated burden

We estimated annual averages of 60 deaths and 284,585 health care utilization episodes for cellulitis. The disease burden from YLL and YERF was relatively even. Disease burden was slightly higher in females, and mainly affected individuals aged 40 or older.

C.9 ENCEPHALITIS

Encephalitis is acute inflammation of the brain. Encephalitis is generally caused by viruses, with herpes simplex virus (HSV) the most common cause, but can also be caused by bacteria. Patients with encephalitis often present with fever, headache and drowsiness and may also have sensitivity to light. Seizures can also occur in patients with encephalitis. Treatment is usually focused on minimizing the symptoms of encephalitis, such as corticosteroids to reduce brain swelling and inflammation, and anticonvulsants to prevent seizures. Antivirals are given when the causative agent has been shown to respond to treatment—primarily acyclovir for herpes simplex virus.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to encephalitis. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for encephalitis. We used epidemiologic studies to determine the percentage of encephalitis caused by various pathogens and the duration of illness that encephalitis typically causes with adequate treatment.

Exhibit C.9
Parameters for estimating the disease burden due to encephalitis

Infectious Agent	Percentage of Encephalitis Attributable to Infectious Agent	Number of Encephalitis Episodes Attributable to Infectious Agent	Number of Encephalitis Deaths Attributable to Infectious Agent
HSV	20[109]	224	4
Other pathogens	80	898	13

Estimated burden

We estimated annual averages of 17 deaths and 1,122 health care utilization episodes for encephalitis. Most of the disease burden was fro m YLL. Disease burden was slightly higher among females and was distributed relatively equally among age groups.

C.10 OTITIS MEDIA

Otitis media is the inflammation of the middle ear, which is usually caused by respiratory viruses but can also result from bacterial infection. Cases of otitis media are often accompanied by upper respiratory tract infections. The most common symptoms of otitis media are earache and fever. Most otitis media is caused by viruses and will resolve without treatment, although analgesics may be used to treat the pain. Acute bacterial otitis media may be treated with antibiotics if symptoms do not dissipate after three days.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to otitis media. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for otitis media. We used epidemiologic studies to determine the percentage of otitis media by various pathogens and the duration of illness that otitis media typically causes with adequate treatment.

Exhibit C.10
Parameters for estimating the disease burden due to otitis media

Infectious Agent	Percentage of Otitis Media Attributable to Infectious Agent	Number of Otitis Media Episodes Attributable to Infectious Agent	Number of Otitis Media Deaths Attributable to Infectious Agent
S. pneumoniae	26[45]	194,420	0
Respiratory syncytial virus	15[113]	112,165	0
H. influenzae	13[44]	97,210	0
Parainfluenza	6.5[113]	48,605	0
Influenza	5[113]	37,388	0
Adenovirus	5[113]	37,388	0
Rhinovirus	1[116]	7,478	0
Other pathogens	29.5	213,114	0

Estimated burden

We estimated annual averages of 0 deaths and 747,768 health care utilization episodes for otitis media. The entire disease burden was from YERF. Disease burden was equal between males and females and affected mostly children from birth to 14 years.

C.11 OSTEOMYELITIS

Osteomyelitis is the infection and subsequent inflammation of the bone and/or bone marrow. Bone infections can develop from microorganisms carried through the bloodstream or contiguous spread from wounds, such as diabetic foot ulcers, surgery or trauma. The symptoms of osteomyelitis can sometime be difficult to recognize or distinguish from other health conditions. Generally, there will be pain in the area of infection, as well as swelling, warmth and redness over the area of infection. Osteomyelitis can also lead to reduction in the use of the extremity where the infection has occurred. Osteomyelitis is treated with a long course of antibiotics, sometimes lasting months, and some cases may require surgical debridement of damaged tissue.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to osteomyelitis. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for osteomyelitis. We used epidemiologic studies to determine the percentage of osteomyelitis by various pathogens and the duration of illness that osteomyelitis typically causes with adequate treatment.

Exhibit C.11
Parameters for estimating the disease burden due to osteomyelitis

Infectious Agent	Percentage of Osteomyelitis Attributable to Infectious Agent	Number of Osteomyelitis Episodes Attributable to Infectious Agent	Number of Osteomyelitis Deaths Attributable to Infectious Agent
S. aureus	50[55]	4,575	18
Group B streptococcus	2[55]	183	1
Other pathogens	48	4,392	18

Estimated burden

We estimated annual averages of 37 deaths and 9,150 health care utilization episodes for osteomyelitis. Most of the disease burden was from YLL. Disease burden was slightly higher in females and mainly affected individuals aged 65 or older.

C.12 NECROTIZING FASCIITIS

Necrotizing fasciitis, or "flesh-eating disease," is a rare infection of the fascial plane, which includes the deepest layers of skin and subcutaneous tissue. The infection normally starts at the site of trauma and progresses rapidly. The patient will experience intense pain, and the skin will become red and swollen. Skin colour will progress to a violet colour with the necrosis of surrounding subcutaneous tissue. Patients commonly experience diarrhea, vomiting and fever. In most cases, necrotizing fasciitis will lead to death without medical intervention. Intravenous antibiotics should be started as soon as the condition is suspected but changed once the causative agent is determined. Urgent surgical debridement of damaged tissue is crucial, and amputation may be necessary in some cases.

Data sources and HALY calculation

For YLL, Ontario vital statistics data were used to determine the number of deaths due to necrotizing fasciitis. For YERF, Ontario health care utilization data were used to identify the number of episodes of care for necrotizing fasciitis. Epidemiologic studies were used to determine the percentage of necrotizing fasciitis by various pathogens and the duration of illness that necrotizing fasciitis typically causes with adequate treatment.

Exhibit C.12
Parameters for estimating the disease burden due to necrotizing fasciitis

Infectious Agent	Percentage of Necrotizing Fasciitis Attributable to Infectious Agent	Number of Necrotizing Fasciitis Episodes Attributable to Infectious Agent	Number of Necrotizing Fasciitis Deaths Attributable to Infectious Agent
Group A streptococcus	22[64]	54	4
Other pathogens	78	191	15

Estimated burden

We estimated annual averages of 19 deaths and 245 health care utilization episodes for necrotizing fasciitis. Most of the disease burden from YLL. Disease burden was slightly higher in females and was distributed relatively evenly among age groups.

C.13 PHARYNGITIS

Pharyngitis is inflammation of the throat (pharynx). It is the most common cause of sore throat and can also be accompanied by a cough and/or fever. Chronic infection can lead to inflammation and swelling of the tonsils, which causes breathing and swallowing difficulty. Treatment for pharyngitis typically involves reducing the symptoms associated with infection, although antibiotics may be given if a bacterial etiology such as Group A streptococcus is established/suspected.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to pharyngitis. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for pharyngitis. We used epidemiologic studies to determine the percentage of pharyngitis by various pathogens and the duration of illness that pharyngitis typically causes with adequate treatment.

Exhibit C.13
Parameters for estimating the disease burden due to pharyngitis

Infectious Agent	Percentage of Pharyngitis Attributable to Infectious Agent	Number of Pharyngitis Episodes Attributable to Infectious Agent	Number of Pharyngitis Deaths Attributable to Infectious Agent
Group A streptococcus	22.5 (0–14 years) 7.5 (≥15 years)[68]	34,647	0
Other pathogens	77.5 (0–14 years) 92.5 (≥15 years)	221,030	1

Estimated burden

We estimated annual averages of one death and 255,677 health care utilization episodes for pharyngitis. Most of the disease burden was from YERF. Disease burden was slightly higher in females, and most of the burden occurred in individuals aged 0–44 years.

C.14 SEPTIC ARTHRITIS

Septic arthritis is an infection of the joint that causes local inflammation which produces arthritis symptoms. Infection of the joint may occur when pathogens circulating in the bloodstream or from nearby infected tissue reach the joint space. Acute onset of intense joint pain and swelling and loss of mobility of the joint are the cardinal symptoms, and cases may also present with fever. Intravenous antibiotics are normally used to treat joint infections. Frequent aspiration or surgical intervention is often required to remove infected synovial fluid.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to septic arthritis. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for septic arthritis. We used epidemiologic studies to determine the percentage of septic arthritis by various pathogens and the duration of illness that septic arthritis typically causes with adequate treatment.

Exhibit C.14
Parameters for estimating the disease burden due to septic arthritis

Infectious Agent	Percentage of Septic Arthritis Attributable to Infectious Agent	Number of Septic Arthritis Episodes Attributable to Infectious Agent	Number of Septic Arthritis Deaths Attributable to Infectious Agent
S. aureus	37[40]	1,299	6
Group A streptococcus	16[40]	562	3
Group B streptococcus	10[60, 61]	351	2
Other gram-positive bacteria	5[40]	176	1
H. influenzae	1[40]	35	0
S. pneumoniae	1[40]	35	0
Other pathogens	30	1,053	5

Estimated burden

We estimated annual averages of 17 deaths and 3,511 health care utilization episodes for septic arthritis. Most of the disease burden was from YLL. Disease burden was equal between males and females, and mainly affected individuals aged 65 or older.

C.15 CONJUNCTIVITIS

Conjunctivitis involves acute inflammation of the outermost layer of the eye and the inner surface of the eyelid (conjunctiva). The inflammation can be the result of an allergic reaction or a viral or bacterial infection. Redness, irritation and watering of the eyes are all common symptoms of conjunctivitis. Cases of infective conjunctivitis typically resolve without treatment, although if no improvement is seen after three days, antibiotics may be prescribed if a bacterial cause is suspected.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to conjunctivitis. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for conjunctivitis. We used epidemiologic studies to determine the percentage of conjunctivitis by various pathogens and the duration of illness that conjunctivitis typically causes with adequate treatment.

Exhibit C.15
Parameters for estimating the disease burden due to conjunctivitis

Infectious Agent	Percentage of Conjunctivitis Attributable to Infectious Agent	Number of Conjunctivitis Episodes Attributable to Infectious Agent	Number of Conjunctivitis Deaths Attributable to Infectious Agent
Adenovirus	20[46]	81,613	0
Streptococcus pneumoniae	12[46]	48,968	0
Other pathogens	68	277,484	0

Estimated burden

We estimated annual averages of 0 deaths and 408,064 health care utilization episodes for conjunctivitis. The entire disease burden was from YERF. Disease burden was slightly higher in females and distributed relatively evenly among age groups.

C.16 BRONCHIOLITIS

Bronchiolitis is the inflammation of the bronchioles—the small branches of the bronchi that lead to the air spaces. Bronchiolitis is usually caused by viruses and mainly affects infants and young children. Cough, wheezing and difficulty breathing are typical symptoms of bronchiolitis, and in serious cases, the infant's/child's skin may turn bluish due to the lack of oxygen (cyanosis). There is no treatment for bronchiolitis, but supportive treatment may be given to ensure adequate oxygen and hydration.

Data sources and HALY calculation

For YLL, we used Ontario vital statistics data to determine the number of deaths due to bronchiolitis. For YERF, we used Ontario health care utilization data to identify the number of episodes of care for bronchiolitis. We used epidemiologic studies to determine the percentage of bronchiolitis caused by various pathogens and the duration of illness that bronchiolitis typically causes with adequate treatment.

Exhibit C.16
Parameters for estimating the disease burden due to bronchiolitis

Infectious Agent	Percentage of Bronchiolitis Attributable to Infectious Agent	Number of Bronchiolitis Episodes Attributable to Infectious Agent	Number of Bronchiolitis Deaths Attributable to Infectious Agent
Respiratory syncytial virus	64[111]	5,613	0
Rhinovirus	16[111]	1,403	0
Adenovirus	7.5[120]	658	0
Influenza	6[111]	526	0
Other pathogens	6.5	570	0

Estimated burden

We estimated annual averages of 0 deaths and 8,770 health care utilization episodes for bronchiolitis. The entire disease burden was from YERF. Disease burden was slightly higher in males and only affected children aged from birth to four years.

Appendix D

International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) Codes Used to Extract Data from Health Care Utilization and Mortality Databases

Exhibit D.1

International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
Acute bronchitis	466		Acute bronchitis
		J200	Acute bronchitis due to *Mycoplasma pneumoniae*
		J201	Acute bronchitis due to *Haemophilus influenzae*
		J202	Acute bronchitis due to streptococcus
		J203	Acute bronchitis due to coxsackievirus
		J204	Acute bronchitis due to parainfluenza virus
		J205	Acute bronchitis due to respiratory syncytial virus
		J206	Acute bronchitis due to rhinovirus
		J207	Acute bronchitis due to echovirus
		J208	Acute bronchitis due to other specified organisms
		J209	Acute bronchitis, unspecified
		J22	Unspecified acute lower respiratory infection
Aspergillosis: non-invasive		B441	Other pulmonary aspergillosis
		B449	Aspergillosis, unspecified
Aspergillosis: invasive pulmonary		B440	Invasive pulmonary aspergillosis
Aspergillosis: invasive non-pulmonary		B442	Tonsillar aspergillosis
		B447	Disseminated aspergillosis
		B448	Other forms of aspergillosis
Bacterial meningitis		G000	Haemophilus meningitis
		G001	Pneumococcal meningitis
		G002	Streptococcal meningitis
		G003	Staphylococcal meningitis
		G008	Other bacterial meningitis
		G009	Bacterial meningitis, unspecified
		G01	Meningitis in bacterial diseases classified elsewhere
Blastomycosis: pulmonary		B400	Acute pulmonary blastomycosis
		B401	Chronic pulmonary blastomycosis
		B402	Pulmonary blastomycosis, unspecified
		B409	Blastomycosis, unspecified
Blastomycosis: disseminated		B403	Cutaneous blastomycosis
		B407	Disseminated blastomycosis
		B408	Other forms of blastomycosis
Bronchiolitis		J210	Acute bronchiolitis due to respiratory syncytial virus
		J218	Acute bronchiolitis due to other specified organisms
		J219	Acute bronchiolitis, unspecified
Candidiasis: non-invasive	112		Candidiasis
		B370	Candidal stomatitis
		B371	Pulmonary candidiasis
		B372	Candidiasis of skin and nail

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
		B373	Candidiasis of vulva and vagina
		B374	Candidiasis of other urogenital sites
		B3782	Candidal cheilitis
		B3783	Candidal otitis externa
		B3788	Candidiasis of other sites
		B379	Candidiasis, unspecified
Candidiasis: semi-invasive		B3780	Candidal esophagitis
		B3781	Candidal enteritis
Candidiasis: invasive		B375	Candidal meningitis
		B376	Candidal endocarditis
		B377	Candidal septicaemia
Cellulitis	682		Cellulitis
		L0300	Cellulitis of finger
		L0301	Cellulitis of toe
		L0310	Cellulitis of upper limb
		L0311	Cellulitis of lower limb
		L032	Cellulitis of face
		L0330	Cellulitis of chest wall
		L0331	Cellulitis of abdominal wall
		L0332	Cellulitis of umbilicus
		L0333	Cellulitis of groin
		L0334	Cellulitis of back [any part except buttock]
		L0335	Cellulitis of buttock
		L0336	Cellulitis of perineum
		L0339	Cellulitis of trunk, unspecified
		L038	Cellulitis of other sites
		L039	Cellulitis, unspecified
		L089	Local infection of skin and subcutaneous tissue, unspecified
Cervicitis	616		Cervicitis
		N72	Inflammatory disease of cervix uteri
Conjunctivitis	372		Conjunctivitis
		H100	Mucopurulent conjunctivitis
		H101	Acute atopic conjunctivitis
		H102	Other acute conjunctivitis
		H103	Acute conjunctivitis, unspecified
		H105	Blepharoconjunctivitis
		H108	Other conjunctivitis
		H109	Conjunctivitis, unspecified
		H131	Conjunctivitis in infectious and parasitic diseases classified elsewhere
		H191	Herpesviral keratitis and keratoconjunctivitis
		H192	Keratitis and keratoconjunctivitis in other infectious and parasitic diseases classified elsewhere
Dengue fever		A90	Dengue fever [classical dengue]
		A91	Dengue haemorrhagic fever
Encephalitis	062		Encephalitis, viral, mosquito-borne

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
	323		Encephalitis
		A811	Subacute sclerosing panencephalitis
		A830	Japanese encephalitis
		A831	Western equine encephalitis
		A832	Eastern equine encephalitis
		A833	St. Louis encephalitis
		A834	Australian encephalitis
		A835	California encephalitis
		A836	Rocio virus disease
		A838	Other mosquito-borne viral encephalitis
		A839	Mosquito-borne viral encephalitis, unspecified
		A840	Far Eastern tick-borne encephalitis [Russian spring-summer encephalitis]
		A841	Central European tick-borne encephalitis
		A848	Other tick-borne viral encephalitis
		A849	Tick-borne viral encephalitis, unspecified
		A850	Enteroviral encephalitis
		A851	Adenoviral encephalitis
		A852	Arthropod-borne viral encephalitis, unspecified
		A858	Other specified viral encephalitis
		A86	Unspecified viral encephalitis
		G040	Acute disseminated encephalitis
		G041	Tropical spastic paraplegia
		G042	Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified
		G048	Other encephalitis, myelitis and encephalomyelitis
		G049	Encephalitis, myelitis and encephalomyelitis, unspecified
		G050	Encephalitis, myelitis and encephalomyelitis in bacterial diseases classified elsewhere
		G051	Encephalitis, myelitis and encephalomyelitis in viral diseases classified elsewhere
		G052	Encephalitis, myelitis and encephalomyelitis in other infectious and parasitic diseases classified elsewhere
		G058	Encephalitis, myelitis and encephalomyelitis in other diseases classified elsewhere
Endocarditis		I330	Acute and subacute infective endocarditis
		I339	Acute endocarditis, unspecified
		I38	Endocarditis, valve unspecified
		I398	Endocarditis, valve unspecified, in diseases classified elsewhere
Histoplasmosis	115		Histoplasmosis

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
		B390	Acute pulmonary histoplasmosis capsulati
		B391	Chronic pulmonary histoplasmosis capsulati
		B392	Pulmonary histoplasmosis capsulati, unspecified
		B394	*Histoplasmosis capsulati,* unspecified
		B395	*Histoplasmosis duboisii*
		B399	Histoplasmosis, unspecified
		B393	Disseminated histoplasmosis capsulati
Necrotizing fasciitis		M7260	Necrotizing fasciitis, multiple sites
		M7261	Necrotizing fasciitis, shoulder region
		M7262	Necrotizing fasciitis, upper arm
		M7263	Necrotizing fasciitis, forearm
		M7264	Necrotizing fasciitis, hand
		M7265	Necrotizing fasciitis, pelvic region and thigh
		M7266	Necrotizing fasciitis, lower leg
		M7267	Necrotizing fasciitis, ankle and foot
		M7268	Necrotizing fasciitis, other site
		M7269	Necrotizing fasciitis, unspecified site
Orchitis/Epididymitis	604		Orchitis
		N511	Disorders of testis and epididymis in diseases classified elsewhere
		N4500	Epididymitis with abscess
		N4501	Orchitis with abscess
		N4502	Epididymo-orchitis with abscess
		N4590	Epididymitis
		N4591	Orchitis
		N4592	Epididymo-orchitis
Osteomyelitis	730		Osteomyelitis
		M4620	Osteomyelitis of vertebra, multiple sites in spine
		M4625	Osteomyelitis of vertebra, thoracolumbar region
		M4628	Osteomyelitis of vertebra, sacral and sacrococcygeal region
		M4629	Osteomyelitis of vertebra, unspecified site
		M8600	Acute haematogenous osteomyelitis, multiple sites
		M8601	Acute haematogenous osteomyelitis, shoulder region
		M8602	Acute haematogenous osteomyelitis, upper arm
		M8603	Acute haematogenous osteomyelitis, forearm
		M8604	Acute haematogenous osteomyelitis, hand

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
		M8605	Acute haematogenous osteomyelitis, pelvic region and thigh
		M8606	Acute haematogenous osteomyelitis, lower leg
		M8607	Acute haematogenous osteomyelitis, ankle and foot
		M8608	Acute haematogenous osteomyelitis, other site
		M8609	Acute haematogenous osteomyelitis, unspecified site
		M8610	Other acute osteomyelitis, multiple sites
		M8611	Other acute osteomyelitis, shoulder region
		M8612	Other acute osteomyelitis, upper arm
		M8613	Other acute osteomyelitis, forearm
		M8614	Other acute osteomyelitis, hand
		M8615	Other acute osteomyelitis, pelvic region and thigh
		M8616	Other acute osteomyelitis, lower leg
		M8617	Other acute osteomyelitis, ankle and foot
		M8618	Other acute osteomyelitis, other site
		M8619	Other acute osteomyelitis, unspecified site
		M8620	Subacute osteomyelitis, multiple sites
		M8621	Subacute osteomyelitis, shoulder region
		M8622	Subacute osteomyelitis, upper arm
		M8623	Subacute osteomyelitis, forearm
		M8624	Subacute osteomyelitis, hand
		M8625	Subacute osteomyelitis, pelvic region and thigh
		M8626	Subacute osteomyelitis, lower leg
		M8627	Subacute osteomyelitis, ankle and foot
		M8628	Subacute osteomyelitis, other site
		M8629	Subacute osteomyelitis, unspecified site
		M8630	Chronic multifocal osteomyelitis, multiple sites
		M8631	Chronic multifocal osteomyelitis, shoulder region
		M8632	Chronic multifocal osteomyelitis, upper arm
		M8633	Chronic multifocal osteomyelitis, forearm
		M8634	Chronic multifocal osteomyelitis, hand
		M8635	Chronic multifocal osteomyelitis, pelvic region and thigh

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
		M8636	Chronic multifocal osteomyelitis, lower leg
		M8637	Chronic multifocal osteomyelitis, ankle and foot
		M8638	Chronic multifocal osteomyelitis, other site
		M8639	Chronic multifocal osteomyelitis, unspecified site
		M8640	Chronic osteomyelitis with draining sinus, multiple sites
		M8641	Chronic osteomyelitis with draining sinus, shoulder region
		M8642	Chronic osteomyelitis with draining sinus, upper arm
		M8643	Chronic osteomyelitis with draining sinus, forearm
		M8644	Chronic osteomyelitis with draining sinus, hand
		M8645	Chronic osteomyelitis with draining sinus, pelvic region and thigh
		M8646	Chronic osteomyelitis with draining sinus, lower leg
		M8647	Chronic osteomyelitis with draining sinus, ankle and foot
		M8648	Chronic osteomyelitis with draining sinus, other site
		M8649	Chronic osteomyelitis with draining sinus, unspecified site
		M8650	Other chronic haematogenous osteomyelitis, multiple sites
		M8651	Other chronic haematogenous osteomyelitis, shoulder region
		M8652	Other chronic haematogenous osteomyelitis, upper arm
		M8653	Other chronic haematogenous osteomyelitis, forearm
		M8654	Other chronic haematogenous osteomyelitis, hand
		M8655	Other chronic haematogenous osteomyelitis, pelvic region and thigh
		M8656	Other chronic haematogenous osteomyelitis, lower leg
		M8657	Other chronic haematogenous osteomyelitis, ankle and foot
		M8658	Other chronic haematogenous osteomyelitis, other site
		M8659	Other chronic haematogenous osteomyelitis, unspecified site
		M8660	Other chronic osteomyelitis, multiple sites
		M8661	Other chronic osteomyelitis, shoulder region
		M8662	Other chronic osteomyelitis, upper arm
		M8663	Other chronic osteomyelitis, forearm
		M8664	Other chronic osteomyelitis, hand

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
		M8665	Other chronic osteomyelitis, pelvic region and thigh
		M8666	Other chronic osteomyelitis, lower leg
		M8667	Other chronic osteomyelitis, ankle and foot
		M8668	Other chronic osteomyelitis, other site
		M8669	Other chronic osteomyelitis, unspecified site
		M8680	Other osteomyelitis, multiple sites
		M8681	Other osteomyelitis, shoulder region
		M8682	Other osteomyelitis, upper arm
		M8683	Other osteomyelitis, forearm
		M8684	Other osteomyelitis, hand
		M8685	Other osteomyelitis, pelvic region and thigh
		M8686	Other osteomyelitis, lower leg
		M8687	Other osteomyelitis, ankle and foot
		M8688	Other osteomyelitis, other site
		M8689	Other osteomyelitis, unspecified site
		M8690	Osteomyelitis, unspecified, multiple sites
		M8691	Osteomyelitis, unspecified, shoulder region
		M8692	Osteomyelitis, unspecified, upper arm
		M8693	Osteomyelitis, unspecified, forearm
		M8694	Osteomyelitis, unspecified, hand
		M8695	Osteomyelitis, unspecified, pelvic region and thigh
		M8696	Osteomyelitis, unspecified, lower leg
		M8697	Osteomyelitis, unspecified, ankle and foot
		M8698	Osteomyelitis, unspecified, other site
		M8699	Osteomyelitis, unspecified, unspecified site
Otitis media	381		Otitis media, serous
	382		Otitis media, suppurative
		H650	Acute serous otitis media
		H651	Other acute nonsuppurative otitis media
		H652	Chronic serous otitis media
		H653	Chronic mucoid otitis media
		H654	Other chronic nonsuppurative otitis media
		H659	Nonsuppurative otitis media, unspecified
		H660	Acute suppurative otitis media
		H661	Chronic tubotympanic suppurative otitis media

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
		H662	Chronic atticoantral suppurative otitis media
		H663	Other chronic suppurative otitis media
		H664	Suppurative otitis media, unspecified
		H669	Otitis media, unspecified
		H670	Otitis media in bacterial diseases classified elsewhere
		H671	Otitis media in viral diseases classified elsewhere
		H678	Otitis media in other diseases classified elsewhere
Pelvic inflammatory disease	614		Acute or chronic salpingitis or oophoritis or abscess
	615		Acute or chronic endometritis
		N700	Acute salpingitis and oophoritis
		N701	Chronic salpingitis and oophoritis
		N709	Salpingitis and oophoritis, unspecified
		N710	Acute inflammatory disease of uterus
		N711	Chronic inflammatory disease of uterus
		N719	Inflammatory disease of uterus, unspecified
		N741	Female tuberculous pelvic inflammatory disease
		N742	Female syphilitic pelvic inflammatory disease
		N743	Female gonococcal pelvic inflammatory disease
		N744	Female chlamydial pelvic inflammatory disease
		N748	Female pelvic inflammatory disorders in other diseases classified elsewhere
Pharyngitis	034		Streptococcal sore throat, scarlet fever
		J020	Streptococcal pharyngitis
		J028	Acute pharyngitis due to other specified organisms
		J029	Acute pharyngitis, unspecified
		J030	Streptococcal tonsillitis
		J038	Acute tonsillitis due to other specified organisms
		J039	Acute tonsillitis, unspecified
Pneumocystosis		B59	Pneumocystosis
Pneumonia	486		Pneumonia, all types
		J100	Influenza with pneumonia, influenza virus identified
		J110	Influenza with pneumonia, virus not identified
		J120	Adenoviral pneumonia
		J121	Respiratory syncytial virus pneumonia
		J122	Parainfluenza virus pneumonia
		J128	Other viral pneumonia
		J129	Viral pneumonia, unspecified

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
		J13	Pneumonia due to *Streptococcus pneumoniae*
		J14	Pneumonia due to *Haemophilus influenzae*
		J150	Pneumonia due to *Klebsiella pneumoniae*
		J151	Pneumonia due to *Pseudomonas*
		J152	Pneumonia due to *Staphylococcus*
		J153	Pneumonia due to streptococcus, group B
		J154	Pneumonia due to other streptococci
		J155	Pneumonia due to *Escherichia coli*
		J156	Pneumonia due to other aerobic gram-negative bacteria
		J157	Pneumonia due to *Mycoplasma pneumoniae*
		J158	Other bacterial pneumonia
		J159	Bacterial pneumonia, unspecified
		J160	Chlamydial pneumonia
		J168	Pneumonia due to other specified infectious organisms
		J170	Pneumonia in bacterial diseases classified elsewhere
		J171	Pneumonia in viral diseases classified elsewhere
		J172	Pneumonia in mycoses
		J173	Pneumonia in parasitic diseases
		J178	Pneumonia in other diseases classified elsewhere
		J180	Bronchopneumonia, unspecified
		J181	Lobar pneumonia, unspecified
		J182	Hypostatic pneumonia, unspecified
		J188	Other pneumonia, organism unspecified
		J189	Pneumonia, unspecified
Septic arthritis	711		Pyogenic arthritis
		M0000	Staphylococcal arthritis and polyarthritis, multiple sites
		M0001	Staphylococcal arthritis and polyarthritis, shoulder region
		M0002	Staphylococcal arthritis and polyarthritis, upper arm
		M0003	Staphylococcal arthritis and polyarthritis, forearm
		M0004	Staphylococcal arthritis and polyarthritis, hand
		M0005	Staphylococcal arthritis and polyarthritis, pelvic region and thigh
		M0006	Staphylococcal arthritis and polyarthritis, lower leg
		M0007	Staphylococcal arthritis and polyarthritis, ankle and foot

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
		M0008	Staphylococcal arthritis and polyarthritis, other site
		M0009	Staphylococcal arthritis and polyarthritis, unspecified site
		M0010	Pneumococcal arthritis and polyarthritis, multiple sites
		M0011	Pneumococcal arthritis and polyarthritis, shoulder region
		M0012	Pneumococcal arthritis and polyarthritis, upper arm
		M0013	Pneumococcal arthritis and polyarthritis, forearm
		M0014	Pneumococcal arthritis and polyarthritis, hand
		M0015	Pneumococcal arthritis and polyarthritis, pelvic region and thigh
		M0016	Pneumococcal arthritis and polyarthritis, lower leg
		M0017	Pneumococcal arthritis and polyarthritis, ankle and foot
		M0018	Pneumococcal arthritis and polyarthritis, other site
		M0019	Pneumococcal arthritis and polyarthritis, unspecified site
		M0020	Other streptococcal arthritis and polyarthritis, multiple sites
		M0021	Other streptococcal arthritis and polyarthritis, shoulder region
		M0022	Other streptococcal arthritis and polyarthritis, upper arm
		M0023	Other streptococcal arthritis and polyarthritis, forearm
		M0024	Other streptococcal arthritis and polyarthritis, hand
		M0025	Other streptococcal arthritis and polyarthritis, pelvic region and thigh
		M0026	Other streptococcal arthritis and polyarthritis, lower leg
		M0027	Other streptococcal arthritis and polyarthritis, ankle and foot
		M0028	Other streptococcal arthritis and polyarthritis, other site
		M0029	Other streptococcal arthritis and polyarthritis, unspecified site
		M0080	Arthritis and polyarthritis due to other specified bacterial agents, multiple sites
		M0081	Arthritis and polyarthritis due to other specified bacterial agents, shoulder region
		M0082	Arthritis and polyarthritis due to other specified bacterial agents, upper arm
		M0083	Arthritis and polyarthritis due to other specified bacterial agents, forearm
		M0084	Arthritis and polyarthritis due to other specified bacterial agents, hand

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
		M0085	Arthritis and polyarthritis due to other specified bacterial agents, pelvic region and thigh
		M0086	Arthritis and polyarthritis due to other specified bacterial agents, lower leg
		M0087	Arthritis and polyarthritis due to other specified bacterial agents, ankle and foot
		M0088	Arthritis and polyarthritis due to other specified bacterial agents, other site
		M0089	Arthritis and polyarthritis due to other specified bacterial agents, unspecified site
		M0090	Pyogenic arthritis, unspecified, multiple sites
		M0091	Pyogenic arthritis, unspecified, shoulder region
		M0092	Pyogenic arthritis, unspecified, upper arm
		M0093	Pyogenic arthritis, unspecified, forearm
		M0094	Pyogenic arthritis, unspecified, hand
		M0095	Pyogenic arthritis, unspecified, pelvic region and thigh
		M0096	Pyogenic arthritis, unspecified, lower leg
		M0097	Pyogenic arthritis, unspecified, ankle and foot
		M0098	Pyogenic arthritis, unspecified, other site
		M0099	Pyogenic arthritis, unspecified, unspecified site
		M0100	Meningococcal arthritis multiple sites
		M0101	Meningococcal arthritis, shoulder region
		M0102	Meningococcal arthritis, upper arm
		M0103	Meningococcal arthritis, forearm
		M0104	Meningococcal arthritis, hand
		M0105	Meningococcal arthritis, pelvic region and thigh
		M0106	Meningococcal arthritis, lower leg
		M0107	Meningococcal arthritis, ankle and foot
		M0108	Meningococcal arthritis, other site
		M0109	Meningococcal arthritis, unspecified site
		M0110	Tuberculous arthritis, multiple sites
		M0111	Tuberculous arthritis, shoulder region
		M0112	Tuberculous arthritis, upper arm
		M0113	Tuberculous arthritis, forearm
		M0114	Tuberculous arthritis, hand
		M0115	Tuberculous arthritis, pelvic region and thigh
		M0116	Tuberculous arthritis, lower leg

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
		M0117	Tuberculous arthritis, ankle and foot
		M0118	Tuberculous arthritis, other site
		M0119	Tuberculous arthritis, unspecified site
		M0120	Arthritis in Lyme disease, multiple sites
		M0121	Arthritis in Lyme disease, shoulder region
		M0122	Arthritis in Lyme disease, upper arm
		M0123	Arthritis in Lyme disease, forearm
		M0124	Arthritis in Lyme disease, hand
		M0125	Arthritis in Lyme disease, pelvic region and thigh
		M0126	Arthritis in Lyme disease, lower leg
		M0127	Arthritis in Lyme disease, ankle and foot
		M0128	Arthritis in Lyme disease, other site
		M0129	Arthritis in Lyme disease, unspecified site
		M0130	Arthritis in other bacterial diseases classified elsewhere, multiple sites
		M0131	Arthritis in other bacterial diseases classified elsewhere, shoulder region
		M0132	Arthritis in other bacterial diseases classified elsewhere, upper arm
		M0133	Arthritis in other bacterial diseases classified elsewhere, forearm
		M0134	Arthritis in other bacterial diseases classified elsewhere, hand
		M0135	Arthritis in other bacterial diseases classified elsewhere, pelvic region and thigh
		M0136	Arthritis in other bacterial diseases classified elsewhere, lower leg
		M0137	Arthritis in other bacterial diseases classified elsewhere, ankle and foot
		M0138	Arthritis in other bacterial diseases classified elsewhere, other site
		M0139	Arthritis in other bacterial diseases classified elsewhere, unspecified site
		M0140	Rubella arthritis, multiple sites
		M0141	Rubella arthritis, shoulder region
		M0142	Rubella arthritis, upper arm
		M0143	Rubella arthritis, forearm
		M0144	Rubella arthritis, hand
		M0145	Rubella arthritis, pelvic region and thigh

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
		M0146	Rubella arthritis, lower leg
		M0147	Rubella arthritis, ankle and foot
		M0148	Rubella arthritis, other site
		M0149	Rubella arthritis, unspecified site
		M0150	Arthritis in other viral diseases classified elsewhere, multiple sites
		M0151	Arthritis in other viral diseases classified elsewhere, shoulder region
		M0152	Arthritis in other viral diseases classified elsewhere, upper arm
		M0153	Arthritis in other viral diseases classified elsewhere, forearm
		M0154	Arthritis in other viral diseases classified elsewhere, hand
		M0155	Arthritis in other viral diseases classified elsewhere, pelvic region and thigh
		M0156	Arthritis in other viral diseases classified elsewhere, lower leg
		M0157	Arthritis in other viral diseases classified elsewhere, ankle and foot
		M0158	Arthritis in other viral diseases classified elsewhere, other site
		M0159	Arthritis in other viral diseases classified elsewhere, unspecified site
		M0160	Arthritis in mycoses, multiple sites
		M0161	Arthritis in mycoses, shoulder region
		M0162	Arthritis in mycoses, upper arm
		M0163	Arthritis in mycoses, forearm
		M0164	Arthritis in mycoses, hand
		M0165	Arthritis in mycoses, pelvic region and thigh
		M0166	Arthritis in mycoses, lower leg
		M0167	Arthritis in mycoses, ankle and foot
		M0168	Arthritis in mycoses, other site
		M0169	Arthritis in mycoses, unspecified sites
		M0180	Arthritis in other infectious and parasitic diseases classified elsewhere, multiple sites
		M0181	Arthritis in other infectious and parasitic diseases classified elsewhere, shoulder region
		M0182	Arthritis in other infectious and parasitic diseases classified elsewhere, upper arm
		M0183	Arthritis in other infectious and parasitic diseases classified elsewhere, forearm
		M0184	Arthritis in other infectious and parasitic diseases classified elsewhere, hand

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
		M0185	Arthritis in other infectious and parasitic diseases classified elsewhere, pelvic region and thigh
		M0186	Arthritis in other infectious and parasitic diseases classified elsewhere, lower leg
		M0187	Arthritis in other infectious and parasitic diseases classified elsewhere, ankle and foot
		M0188	Arthritis in other infectious and parasitic diseases classified elsewhere, other site
		M0189	Arthritis in other infectious and parasitic diseases classified elsewhere, unspecified site
Septicaemia		A021	*Salmonella* septicaemia
		A227	Anthrax septicaemia
		A267	Erysipelothrix septicaemia
		A327	Listerial septicaemia
		A392	Acute meningococcaemia
		A393	Chronic meningococcaemia
		A394	Meningococcaemia, unspecified
		A400	Septicaemia due to streptococcus, group A
		A401	Septicaemia due to streptococcus, group B
		A402	Septicaemia due to streptococcus, group D
		A403	Septicaemia due to *Streptococcus pneumoniae*
		A408	Other streptococcal septicaemia
		A409	Streptococcal septicaemia, unspecified
		A410	Septicaemia due to Staphylococcus aureus
		A411	Septicaemia due to other specified staphylococcus
		A412	Septicaemia due to unspecified staphylococcus
		A413	Septicaemia due to *Haemophilus influenzae*
		A414	Septicaemia due to anaerobes
		A4150	Septicaemia due to *Escherichia coli*
		A4151	Septicaemia due to *Pseudomonas*
		A4152	Septicaemia due to *Serratia*
		A4158	Septicaemia due to other gram-negative organisms
		A4180	Septicaemia due to *Enterococcus*
		A4188	Other specified septicaemia
		A419	Septicaemia, unspecified
		A427	Actinomycotic septicaemia
		B377	Candidal septicaemia
Upper respiratory tract infection	460		Acute nasopharyngitis, common cold

Exhibit D.1 (CONTINUED)
International Classification of Diseases, Tenth Revision (ICD-10) and Ontario Health Insurance Plan (OHIP) codes used to identify episodes of health care utilization

Syndrome	OHIP Code	ICD-10 Code	Description
	464		Acute laryngitis, tracheitis, croup, epiglottitis
		J00	Acute nasopharyngitis [common cold]
		J040	Acute laryngitis
		J041	Acute tracheitis
		J042	Acute laryngotracheitis
		J050	Acute obstructive laryngitis [croup]
		J051	Acute epiglottitis
		J060	Acute laryngopharyngitis
		J068	Other acute upper respiratory infections of multiple sites
		J069	Acute upper respiratory infection, unspecified
Urethritis	597		Nonspecific urethritis
		N340	Urethral abscess
		N341	Nonspecific urethritis
		N342	Other urethritis
		N370	Urethritis in diseases classified elsewhere
Urinary tract infections	590		Acute or chronic pyelonephritis, pyelitis, abscess
	595		Cystitis
	601		Prostatitis
		N10	Acute tubulo-interstitial nephritis
		N12	Tubulo-interstitial nephritis, not specified as acute or chronic
		N151	Renal and perinephric abscess
		N300	Acute cystitis
		N308	Other cystitis
		N309	Cystitis, unspecified
		N410	Acute prostatitis
		N412	Abscess of prostate
		N413	Prostatocystitis
		N510	Disorders of prostate in diseases classified elsewhere
		N390	Urinary tract infection, site not specified
Varicella: acute	052		Chickenpox
		B019	Varicella without complication
Varicella with complications		B010	Varicella meningitis
		B011	Varicella encephalitis
		B012	Varicella pneumonia
		B018	Varicella with other complications
Zoster: acute	053		Herpes zoster, shingles
		B029	Zoster without complication
Zoster with complications		B020	Zoster encephalitis
		B021	Zoster meningitis
		B022	Zoster with other nervous system involvement
		B023	Zoster ocular disease
		B027	Disseminated zoster
		B028	Zoster with other complications

Exhibit D.2
ICD-10 codes used to identify infectious disease deaths in the vital statistics data

Infectious Agent	ICD-10 Code
Adenovirus	
Upper respiratory tract infection	See Exhibit D.1
Otitis media	See Exhibit D.1
Bronchiolitis	See Exhibit D.1
Pneumonia	See Exhibit D.1
Conjuncitivitis	See Exhibit D.1
Aspergillus	
Aspergillosis	See Exhibit D.1
Blastomyces	
Blastomycosis	See Exhibit D.1
Campylobacter	
Campylobacter enteritis	A04.5
Candida	
Canadidiasis	See Exhibit D.1
Chlamydia	
Sexually transmitted chlamydial disease	A55, A56
Pelvic inflammatory disease	See Exhibit D.1
Urethritis	See Exhibit D.1
Cervicitis	See Exhibit D.1
Epididymitis/orchitis	See Exhibit D.1
Ophthalmia neonatorum	P39.1
Clostridium difficile	
Enterocolitis due to *Clostridium difficile*	A04.7
Coronavirus	
Upper respiratory tract infection	See Exhibit D.1
Acute bronchitis	See Exhibit D.1
Cryptosporidium	
Cryptosporidiosis	A07.2

Infectious Agent	ICD-10 Code
Cyclospora	
Other specified protozoal infestinal diseases	A07.8
Dengue	
Dengue fever and dengue heamorrhagic fever	See Exhibit D.1
Diphtheria	
Diphtheria	A36
Escherichia coli	
Bacterial meningitis	See Exhibit D.1
Urinary tract infections	See Exhibit D.1
Septicaemia	See Exhibit D.1
Pneumonia	See Exhibit D.1
E. coli O157	
Enterohaemorrhagic *E. coli* infection	A04.3
Haemolytic-uraemic syndrome	D59.3
Giardia	
Giardiasis	A07.1
Group A streptococcus	
Bacterial meningitis	See Exhibit D.1
Septic arthritis	See Exhibit D.1
Pharyngitis	See Exhibit D.1
Cellulitis	See Exhibit D.1
Necrotizing fasciitis	See Exhibit D.1
Septicaemia	See Exhibit D.1
Pneumonia	See Exhibit D.1
Group B streptococcus	
Bacterial meningitis	See Exhibit D.1
Septicaemia	See Exhibit D.1
Septic arthritis	See Exhibit D.1

Exhibit D.2 (CONTINUED)
ICD-10 codes used to identify infectious disease deaths in the vital statistics data

Infectious Agent	ICD-10 Code
Cellulitis	See Exhibit D.1
Osteomyelitis	See Exhibit D.1
Sepsis of the newborn	P36
Gonorrhea	
Sexually transmitted gonococcal disease	A54, excluding A54.3
Pelvic inflammatory disease	See Exhibit D.1
Urethritis	See Exhibit D.1
Cervicitis	See Exhibit D.1
Epididymitis/orchitis	See Exhibit D.1
Ophthalmia neonatorum	A54.3
Haemophilus influenzae	
Bacterial meningitis	See Exhibit D.1
Septic arthritis	See Exhibit D.1
Septicaemia	See Exhibit D.1
Pneumonia	See Exhibit D.1
Otitis media	See Exhibit D.1
Hepatitis A	
Acute hepatitis A	B15
Hepatitis B virus	
Acute hepatitis B	B16, B17.0
Chornic viral hepatitis B	B18.0, B18.1
Unspecified viral hepatitis	B19
Congenital viral hepatitis	P35.3
Hepato-cellular carcinoma	C22
Hepatic failure	K72
Chronic hepatitis, unspecified	K73.9
Other and unspecified cirrhosis of the liver	K74.6
Portal hypertension or hepatorenal syndrome	K76.6, K76.7
Esophageal varices	I85
Hepatitis C virus	
Acute hepatitis B	B17.1
Chornic viral hepatitis B	B18.2
Unspecified viral hepatitis	B19
Congenital viral hepatitis	P35.3
Hepato-cellular carcinoma	C22
Hepatic failure	K72
Chronic hepatitis, unspecified	K73.9
Other and unspecified cirrhosis of the liver	K74.6
Portal hypertension or hepatorenal syndrome	K76.6, K76.7
Esophageal varices	I85
Herpes virus	
Anogenital herpesviral infection	A60
Herpesviral infection	B00
Neonatal herpes	P35.2
Encephalitis	See Exhibit D.1
Histoplasma	
Histoplasmosis	See Exhibit D.1
HIV/AIDS	
Human immunodeficiency virus disease	B20–B24
Human papillomavirus	
Cervical cancer	C53
Vaginal cancer	C52
Vulval cancer	C51
Penile cancer	C60
Anal cancer	C21

Exhibit D.2 (CONTINUED)
ICD-10 codes used to identify infectious disease deaths in the vital statistics data

Infectious Agent	ICD-10 Code
Oropharyngeal cancer	C01, C024, C051, C052, C09, C10
Influenza	
Otitis media	See Exhibit D.1
Upper respiratory tract infection	See Exhibit D.1
Pneumonia	See Exhibit D.1
Acute bronchitis	See Exhibit D.1
Bronchiolitis	See Exhibit D.1
Influenza	J10.1, J10.8, J11.1, J11.8
Legionella	
Pneumonia	See Exhibit D.1
Listeria	
Listeriosis	A32
Malaria	
Malarial disease	B50–B54
Congenital malaria	P37.3, P37.4
Measles	
Measles	B05
Mumps	
Mumps	B26
Neisseria meningitidis	
Bacterial meningitis	See Exhibit D.1
Parainfluenza virus	
Upper respiratory tract infection	See Exhibit D.1
Otitis media	See Exhibit D.1
Acute bronchitis	See Exhibit D.1
Pneumonia	See Exhibit D.1
Pertussis	
Whooping cough	A37
Pneumocystis jiroveci	
Pneumocystosis	See Exhibit D.1
Poliomyelitis	
Acute poliomyelitis	A80
Sequelae of poliomyelitis	B91
Respiratory syncytial virus	
Upper respiratory tract infection	See Exhibit D.1
Otitis media	See Exhibit D.1
Bronchiolitis	See Exhibit D.1
Acute bronchitis	See Exhibit D.1
Pneumonia	See Exhibit D.1
Rhinovirus	
Upper respiratory tract infection	See Exhibit D.1
Otitis media	See Exhibit D.1
Bronchiolitis	See Exhibit D.1
Acute bronchitis	See Exhibit D.1
Rubella	
Rubella (German measles)	B06
Congenital rubella syndrome	P35.0
Salmonella	
Salmonellosis	A02
Shigella	
Shigellosis	A03
Staphylococcus aureus	
Endocarditis	See Exhibit D.1

Exhibit D.2 (CONTINUED)
ICD-10 codes used to identify infectious disease deaths in the vital statistics data

Infectious Agent	ICD-10 Code
Septicaemia	See Exhibit D.1
Pneumonia	See Exhibit D.1
Septic arthritis	See Exhibit D.1
Osteomyelitis	See Exhibit D.1
Cellulitis	See Exhibit D.1
Streptococcus pneumoniae	
Bacterial meningitis	See Exhibit D.1
Septic arthritis	See Exhibit D.1
Septicaemia	See Exhibit D.1
Pneumonia	See Exhibit D.1
Acute bronchitis	See Exhibit D.1
Otitis media	See Exhibit D.1
Conjuncitivitis	See Exhibit D.1
Syphilis (*Treponema pallidum*)	
Congenital syphilis	A50
Early syhpilis	A51
Late syphilis	A52
Syphilis, unspecified	A53.9
Tetanus	
Tetanus neonatorum	A33
Obstetrical tetanus	A34
Other tetanus	A35
Tuberculosis	
Tuberculosis	A15–A19
Sequelae of tuberculosis	B90
Congenital tuberculosis	P37.0
Typhoid/Paratyphoid	
Typhoid and paratyphoid fevers	A01
Varicella	
Varicella (chickenpox)	See Exhibit D.1
Zoster (herpes zoster)	See Exhibit D.1
Congenital varicella	P35.8
West Nile virus	
West Nile virus infection	A92.3
Yersinia	
Enteritis due to *Yersinia enterocolitica*	A04.6

Acronyms, Exhibits, Authors and Acknowledgements

List of Acronyms

AIDS	Acquired immune deficiency syndrome
CIHI	Canadian Institute for Health Information
CLAMES	Classification and Measurement System of Functional Health
DAD	Discharge Abstract Database
DALY	Disability-adjusted life years
GBD	Global Burden of Disease study
HALYs	Health-adjusted life years
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HPPA	Health Protection and Promotion Act
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
ICD	International Classification of Diseases
ICES	Institute for Clinical Evaluative Sciences
iPHIS	integrated Public Health Information System
LE	Life expectancy
NACRS	National Ambulatory Care Reporting System
OAHPP	Ontario Agency for Health Protection and Promotion
OCR	Ontario Cancer Registry
OHIP	Ontario Health Insurance Plan
ONBODS	Ontario Burden of Disease Study
ONBOIDS	Ontario Burden of Infectious Disease Study
PHI	Population Health Impact of Disease in Canada
QALY	Quality-adjusted life years
RDIS	Reportable Disease Information System
RSV	Respiratory syncytial virus
SARS	Severe acute respiratory syndrome
SW	Severity weight
SDS	Same-day surgery
TB	Tuberculosis
VZV	Varicella zoster virus
WHO	World Health Organization
WNV	West Nile virus
YERF	Year-equivalents of reduced functioning
YLL	Years of life lost to premature mortality
YLD	Years of life lived with a disability

List of Exhibits

List of Exhibits (CONTINUED)

List of Exhibits (CONTINUED)

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ABOUT THE ONTARIO AGENCY FOR HEALTH PROTECTION AND PROMOTION

The Ontario Agency for Health Protection and Promotion (OAHPP) is an arm's-length government agency dedicated to protecting and promoting the health of all Ontarians and reducing inequities in health. As a hub organization, OAHPP links public health practitioners, front-line health workers and researchers to the best scientific intelligence and knowledge from around the world.

OAHPP provides expert scientific and technical support relating to infection prevention and control; surveillance and epidemiology; health promotion, chronic disease and injury prevention; environmental and occupational health; health emergency preparedness; and public health laboratory services to support health providers, the public health system and partner ministries in making informed decisions and taking informed action to improve the health and security of Ontarians.

OAHPP's mission is to support health-care providers, the public health system and partner ministries in making informed decisions and taking informed action to improve the health and security of all Ontarians, through the transparent and timely provision of credible scientific advice and practical tools. To enable this, the focus is on three key goals:

- **Information:** Provide timely, relevant and reliable information for better public health decisions and actions
- **Knowledge:** Generate and accelerate the uptake and application of current evidence-based knowledge in public health decisions and actions
- **Support:** Provide high-quality support to the Ontario public health system in its daily business and enhance capacity in emergencies

Ontario
Agency for Health Protection and Promotion
Agence de protection et de promotion de la santé

ABOUT THE INSTITUTE FOR CLINICAL EVALUATIVE SCIENCES

The Institute for Clinical Evaluative Sciences (ICES) is an independent, non-profit organization that produces knowledge to enhance the effectiveness of health care for Ontarians. Internationally recognized for its innovative use of population-based health information, ICES' evidence supports health policy development and guides changes to the organization and delivery of health care services.

Key to our work is our ability to link population-based health information, at the patient-level, in a way that ensures the privacy and confidentiality of personal health information. Linked databases reflecting 13 million of 33 million allow us to follow patient populations through diagnosis and treatment, and to evaluate outcomes.

ICES brings together the best and the brightest talent from across Ontario. Many of our scientists are not only internationally recognized leaders in their fields but are also practicing clinicians who understand the grassroots of health care delivery, making the knowledge produced at ICES clinically-focused and useful in changing practice. Other team members have statistical training, epidemiological backgrounds, project management or communications expertise. The variety of skill sets and educational backgrounds ensures a multi-disciplinaryapproach to issues and creates a real-world mosaic of perspectives that is vital to shaping Ontario's future health care system.

ICES receives core funding from the Ontario Ministry of Health and Long-Term Care. In addition, our faculty and staff compete for peer-reviewed grants from federal funding agencies, such as the Canadian Institutes of Health Research, and project-specific funds are received from provincial and national organizations. These combined sources enable ICES to have a large number of projects underway, covering a broad range of topics. The knowledge that arises from these efforts is always produced independent of our funding bodies, which is critical to our success as Ontario's objective, credible source of Evidence Guiding Health Care.

ICES Institute for Clinical Evaluative Sciences