Discussion Paper

Assessing the Population Impact of Published Intervention Studies

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**The authors are participants in the activities of the IOM Roundtable on Population Health Improvement*

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ABSTRACT

Background: Despite greater spending on health care and biomedical research, the United States has poorer health outcomes than competitive nations. Information is needed on the potential impact of interventions to better guide resources allocation.

Objective: To assess whether research on interventions is concentrated in areas with the greatest potential population health benefit.

Design: Secondary data analysis to perform a best-case study of the potential population impact of published intervention studies.

Study selection: A random sample of 20 intervention studies published in the *New England Journal of Medicine* in 2011.

Data extraction: One reviewer extracted data using a standardized form, and another reviewer verified the data.

Measurements: The incremental gain of applying the intervention versus the control estimated in quality-adjusted life years (QALY) at the population level.

Results: Of the 20 studies, 13 had a statistically significant effect size, and 3 studies accounted for 80 percent of the total population health impact. Studies of less common conditions had smaller population health impact, though greater individual level impact. Studies generally did not report the information required to estimate the anticipated population health impact.

Limitations: The heterogeneity of outcome measures and the use of multiple data sources result in a large degree of uncertainty in the estimates. The use of an intervention effect measured in a study setting is likely to overestimate its real-world impact. Although random, the sample of studies selected here may not be representative of intervention studies in general.

Conclusions: Research priorities should be heavily informed by the potential population health impact. Researchers, proposal reviewers, and funders should understand those impacts before intervention studies are initiated. We recommend that this information be uniformly included in research proposals and reports.

INTRODUCTION

1 The authors are participants in the activities of the IOM Roundtable on Population Health Improvement .

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Not only does the United States spend more per capita on medical care than any other nation, and more than twice as much as the average for all other countries in the Organisation for Economic Co-operation and Development, it spends more on medical research as well.[1, 2] Yet despite the high level of spending, our health outcomes are mediocre at best; the United States ranks 26th in life expectancy and 31st in infant mortality among developed nations.[3] This discrepancy raises the question about the value derived from the governmental and nongovernmental investments in medical research. In contradistinction to basic science research, for which the goal is arguably to advance science for the development of knowledge, translational science seeks to improve health through the development of bench-to-bedside interventions and to assure their use in patients and populations that would benefit from them. To improve health measurably, translational research needs to focus on identifying interventions that are likely to provide the greatest population health benefit as well as interventions that are widely used but are ineffective or harmful. In a prior paper we proposed a set of criteria for researchers, funders, journal editors, and consumers of research to assess the importance and value of studies on health interventions—to answer the "so what" question.[4] Those criteria include the burden of disease (quality-adjusted life years [QALYs] lost due to the condition), the preventable burden (how much health burden could be alleviated if the intervention were successful), the economic value (cost and cost-effectiveness), and the additional information gained from the study (e.g., sufficient information to change an evidence-based recommendation).

Interventions may be traditional clinical interventions; changes to health care systems; or population-health interventions, such as changes in policy, interventions to address behaviors or underlying social and environmental determinants, or public health programs. Despite their potentially large impacts, population-health interventions are inadequately studied.

There are, of course, many reasons for conducting studies other than their potential aggregate health impact, including the need to address specific rare diseases or improve understanding of disease processes, though we would argue a primary goal of publicly supported research should be to conduct studies of interventions with the clear potential to improve population health and intended to be implemented rapidly. We therefore turned to a leading medical journal known for publishing cutting-edge research to estimate the likely impact of published intervention studies.

METHODS

Sample Selection

We identified original articles describing an intervention study published in *The New England Journal of Medicine* between January and December 2011 (Figure 1). In every other issue, the title and abstract of all original articles were examined to classify articles by study design (descriptive, observational, or experimental [e.g., randomized clinical trial]) and to identify articles describing the evaluation of an intervention. Exclusion criteria included topics of mental health, cost or cost-effectiveness analysis (if there was no assessment of effectiveness), safety assessment, and system-level intervention (e.g., studies of hospital quality improvement systems). A sample of 20 articles was then randomly selected from the studies meeting the criteria. Articles excluded and not selected are listed in Tables A-1 and A-2 in the appendix.

Abstraction

The abstraction protocol was adapted from the methods developed for the *Guide to Community Preventive Services*.[6, 7] We used a standardized form to record information on the nature of the intervention, study population, time horizon, outcome measures, study rationale, and sources of funding (see appendix). In addition, we evaluated articles for the inclusion of information required for calculating the expected population impact of the intervention: burden of disease (incidence, prevalence, and mortality) and expected changes in quality of life. Catherine Chanfreau-Coffinier performed the literature abstraction, and Steven Teutsch reviewed it. We resolved disagreements through consensus.

Population Measures

We performed a best-case study for the expected population impact of the interventions, assuming that all patients with the targeted condition(s) were eligible to receive the treatment and would initiate the treatment. We estimated the total burden of disease and the expected population impact of the interventions using multiple sources of information. Where available we used data presented in the evaluated article. Where data were not included we used (1) statistics from the Centers for Disease Control and Prevention (www.cdc.gov), (2) Cochrane reviews,[3] and (3) high-quality literature, in that order. All values and sources are listed in Table A-3 in the appendix.

Net Health Benefits

Net health benefits were calculated as lives saved and as gains in QALYs. QALYs are a measure of life expectancy in years of life adjusted for the quality of life [QOL], with an adjustment factor ranging from 1 for a perfect health state to 0 for the worst possible health state.[8] Using QALYs allows for the comparison of interventions across diverse health conditions. In our framework, QALYs gained are the differences in QALYs resulting from applying the intervention versus the control procedure in each study. QALYs were calculated using the QOL factors documented in the evaluated article whenever available; otherwise, QOL factors were collected from a comprehensive review by Tengs and Wallace[9] or high-quality QOL or cost-effectiveness literature. All values and sources are listed in Table A-3 in the appendix. The formulas used to estimate population impacts of the intervention are shown in the appendix. QALYs may be gained by saving additional years of life with the intervention and/or by increasing the quality of life over a period of time. In brief, we subtracted the gain in QALYs achieved with the intervention from the gain achieved with the control procedure. In addition, we evaluated average QALYs gained per case and average QALYs gained per life saved, if applicable.

Evaluation of the Intervention Impact at the Patient Level

The expected effect of the intervention per patient was based on the effect size for the primary outcome reported in the study. We assume that the intervention would have the same

[3] The Cochrane Collaboration conducts independent, systematic reviews of evidence to inform health decisions, and their work is available at http://www.cochrane.org/.

effect in real-world practice as found in the study and that the effect size would remain constant over time. The studies assessed were all efficacy studies. Thus the expected impact in practice is likely overestimated. Because many studies had small or null effect sizes, we anticipate they would have an even smaller impact in practice.

The average impact of the intervention (or control procedure) was estimated for a "typical" patient. The life expectancy of the "typical" patient at the time of treatment was based on the average age of the sample in the study, the life expectancy for people of that age reported in the 2009 *United States Life Tables,*[10] and the average loss of life years expected for a patient with that condition.

Evaluation of the Intervention Impact at the Population Level

The impact of the intervention (based on QALYs gained per patient) was then applied to the whole patient population. To ensure the comparability among studies, we performed calculations on the basis of the current burden of disease. When available, we included information on the treatment uptake and adherence as reported in the studies and incorporated those factors to estimate treatment effectiveness. We calculated the average QALY gain per patient as the total number of QALYs gained for an intervention divided by the number of cases expected for the condition.

To account for the inherent uncertainty, we calculated all point estimates for the population impact of the intervention using the lower and upper bound values for the variables following the methods of the *Guide to Community Preventive Services*.[6, 7]

RESULTS

We examined 106 original articles describing an intervention study in 26 issues of *The New England Journal of Medicine* published from January to December 2011 (Figure 1). On the basis of our selection criteria, we identified 64 eligible articles and excluded five articles: three safety studies, one mental health intervention, and one system intervention (Table A-1). Random selection of 20 articles among the 59 included resulted in 20 randomized controlled trial (RCT) studies (the articles not selected are listed in Table A-2).

Most studies were U.S.-based; only six were non-U.S. or international studies. Funding sources were diverse, with nine studies publicly funded, six studies funded by industry, and five with both public and industry funding. Three studies are secondary analyses of large clinical trials.[11–13] Although the rationale for each study was clearly documented by the authors, information necessary to evaluate the burden of disease was present in only 50 percent of the articles, and only one study documented quality of life, which was the primary outcome of the intervention.[13]

We used the information summarized in Table A-3 to calculate the expected population impact of the intervention compared to the control procedures. The minimum and maximum expected values were calculated by applying the intervention to the entire eligible patient population (Table 1). Calculations were performed only for the 13 interventions that found a significant difference in effect between the intervention and the control procedure. The estimated effect sizes vary greatly both in magnitude and in uncertainty across studies (Figure 2). Some of the variations reflect differences in the patient population that may benefit from the intervention:

if the eligible patient population is large, even a modest intervention effect may result in a large gain in total QALYs. Consequently, we find that a small number of interventions account for the majority of the population impact, with three of the interventions accounting for more than 80 percent of all expected gains in QALYs. In contrast, the six interventions with the lowest impact produced an expected total QALY gain of less than 1 percent, or 100,000 QALYs.

When viewed on a per patient basis, many of the interventions were found to have a small effect. The exceptions were the cases of less common conditions (type 1 diabetes,[14] aplastic anemia,[15] and Turner syndrome[16]) for which interventions were found to have a large impact at the individual level.

DISCUSSION

We estimated the likely population impact of intervention studies published in a preeminent journal. A significant difference in effect between the intervention and the control procedure was found in only 13 of the 20 evaluated studies. We observed a wide variation in effect sizes across the studies, both in magnitude and in uncertainty. In particular, we found that most interventions with large population-level impact had a modest intervention effect at the individual level, whereas several interventions for less common or rare conditions had small population effects, but relatively large patient-level impact. Therefore, both population-based and patient-based measures are important to consider, as they may result in very different ranking of the impacts.[17]

The National Commission on Prevention Priorities has assessed the population impact of clinical preventive services recommended by the U.S. Preventive Services Task Force,[18] the Agency for Healthcare Research and Quality has assessed the effectiveness of care, and the Patient Centered Outcomes Research Institute has prioritized important clinical care questions. A recent National Heart, Lung, and Blood Institute study showed large differences in the potential impacts of trials it sponsored.[5] We believe that translational research should focus on those interventions with the greatest potential population health impact.

By systematically sampling 20 intervention studies from a single leading medical journal, all of which were randomized trials, we have demonstrated the feasibility of assessing population health impacts if the study interventions were to be adopted in practice. Remarkably, few of the studies actually report the information needed to assess the population impact, though we were able to obtain the data needed from other sources. Even fewer calculate the overall population impact, and they rarely provide cost or comparisons of costs to health or economic benefits. The lack of this information means reviewers and readers must infer the relevant population and basic information such as the baseline life expectancy and quality of life. It is reasonable to expect researchers to determine or at least estimate the impacts they anticipated prior to embarking on intervention studies. Their ability to do so would be significantly enhanced by more standardized and accessible values for quality of life.

We assessed the incremental value of the interventions compared to the control procedures used in the trials. Choice of trial comparator is of singular importance, and selection of placebo or suboptimal therapy as comparators will overstate the potential impact of interventions. To understand the importance and incremental value of the intervention, trial comparators should include the best available, most reasonable alternative. This was not always the case.

LIMITATIONS

This study has a number of important limitations. The studies included represent a small sample of intervention studies, all of which were published in the same journal in the same year. Thus they may reflect the selection criteria of the journal or may not be representative of intervention studies more generally. Several sources were used to obtain parameter estimates for calculating the population impact, and these sources do not use consistent methods. All studies in our sample were randomized trials, and selection criteria used in each study limit their generalizability to the population as a whole and likely overestimate adherence in both the intervention and control groups. In addition, studies are of limited duration, so estimating long-term effects adds uncertainty. In each case, however, we erred on the side of choosing parameters that would provide the greatest potential impact. Hence, these results are "best case" scenarios that provide an upper bound on population health impacts; real-world impacts are likely to be smaller. Despite these limitations, there are very large differences in population health impact among the studies, differences not plausibly due to methodological decisions or uncertainty. What is apparent is that most studies have at best small or no population health effects and that a small number have substantial population effects.

Three studies were secondary analyses of already-published RCTs. In those cases, we did not assess the impact of the trials as a whole, but rather assessed the effect of the secondary analysis. Although we believe our estimates of population health impacts are reasonable, there is variability in the underlying parameters (e.g., variations by ethnic or racial groups, by geography, or in the definition of certain conditions) and data sources (e.g., estimates can come from cross-sectional studies or clinical environments, be self-reported, be clinician diagnosed, or have definitive diagnoses). These variations introduce uncertainty into the assessment process, and thus the findings should be considered estimates rather than precise determinations. In addition, there are differences in timing of benefits and harms and differential impacts among population groups. Consequently, small differences among studies we examined should be interpreted with caution. In prior work[18] the population health impact of recommended clinical preventive services differed by several orders of magnitude and services were grouped into five impact categories to reduce attention to small differences among them and to emphasize the enormous, often poorly understood differences in effectiveness and cost-effectiveness. As the number of studies assessing the population health accumulates, a similar approach could minimize overinterpretation of small differences.

We studied the results of published studies, not the original research proposals themselves. Nonetheless, the likelihood of finding little population effect could often have reasonably been anticipated beforehand. The secondary analyses of previously published trials might have been done to expand indications, potentially to identify a subgroup for which use of a technology found ineffective in the primary analysis could be justified.

Because of the limited resources for research, we must always make choices about which studies to conduct. The paucity of studies of population health interventions (policies and programs) reflects both the research priorities of decision makers as well as the complexity of conducting such studies. We believe that research priorities should be heavily informed by the potential population health impact and that researchers, proposal reviewers, and funders need to understand those impacts before intervention studies are initiated. This approach was recently

used to estimate the expected value of a proposed study[19] and to justify the undertaking of a new controlled trial.[20] To that end, we recommend that the information necessary to estimate the impact of the proposed intervention be uniformly included in research proposals and reports. All requests for proposals of interventions should explicitly require that study proposals project the population health impact of the study using standard procedures such as those we used, and funders should assess the projections and use them in funding decisions. Journals should require that the information be included in reports of intervention studies, and reviewers should be tasked with evaluating the adequacy of the assessments. The addition of this new component in the peer-review process will likely require additional training of the reviewers. By the same token, journals should insist that this information be conveyed effectively to readers so the latter can use the results more effectively. Constant attention to the "so what" question should help direct our public translational research investments in ways that provide the greatest good for the investors and primary beneficiaries, the American public.

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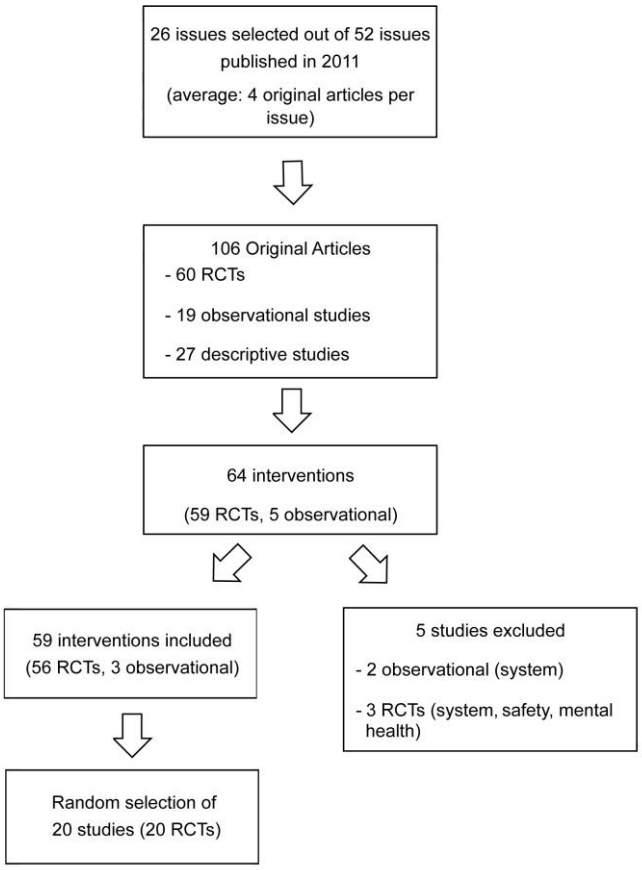

FIGURE 1 Flow chart describing the sample selection.

NOTE: RCT, randomized controlled trial.

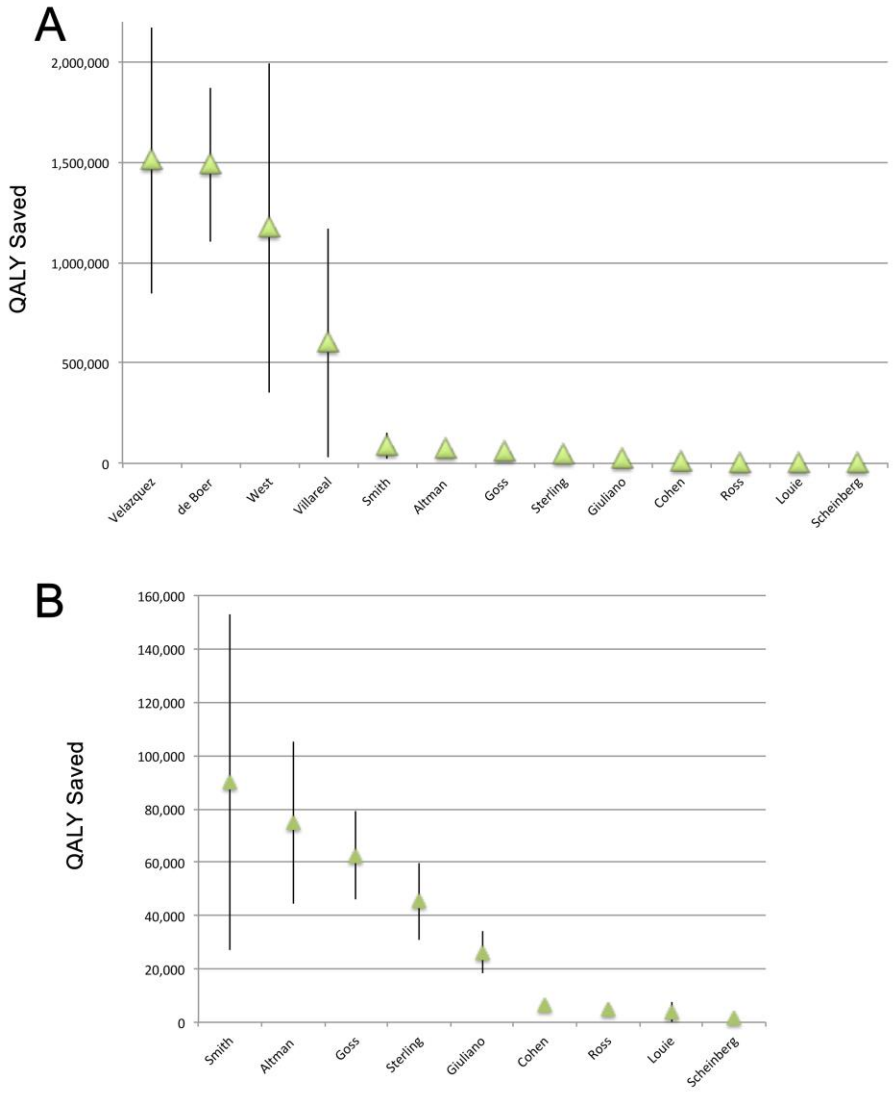

FIGURE 2 Estimates of the expected population-level benefit of using the intervention compared to the control procedure.

NOTES: A. Plot featuring the studies with a significant intervention impact. Numeric values for all estimates are shown in Table 1 as minimum and maximum values for the total quality-adjusted life year (QALY) gains resulting from improved quality of life and saved lives. Triangles indicate the average value of the estimates, and the bars indicate the width of the interval. B. Higher magnification for the interventions estimated to result in an average gain of less than 200,000 QALYs.
See Table 1 for reference numbers for authors' full source citations.

TABLE 1 Expected Population Impact Gained from Applying the Intervention Compared to the Control

Publication	Condition: Treatment and Control Procedure	Outcome	Gain in Effect (intervention vs. control procedure)	Lives Saved	QALYs Gained from Lives Saved	QALYs Gained from Greater Quality of Life	Total QALYs Gained	Average QALY Gain per Patient
Velazquez[21]	Left ventricular dysfunction: Bypass surgery (CABG) with medical therapy vs. medical therapy alone	All-cause mortality at > 2-year follow-up	Risk reduction = 0–6% (based on mortality HR = 0.86 [.72, 1.04])	0–12,735	0–220,061	849,000–1,952,700	849,000–2,172,761	1.78
de Boer[14]	Renal function in type 1 diabetes: intensive or conventional diabetes management	Impairment of kidney glomerular filtration	Risk reduction for end-stage renal disease: 50% [18%, 69%]	20,124–30,186	603,720–905,580	503,100–967,500	1,106,820–1,873,080	10.13
West[22]	Smoking cessation: Cytisine vs. placebo	Sustained abstinence at 12 months	6% increase in smoking cessation at 12 months	416,420	[direct estimation of total QALYs]	[direct estimation of total QALYs]	355,500–1,990,800	0.05
Villareal[23]	Obesity in older adults: weight loss, physical activity, or both	Change in score on the modified Physical Performance Test (PPT)	Significant increase in PPT score, with an average loss of 4 BMI points and a change in obesity class [Average BMI at baseline = 37; average BMI after intervention = 33]	[direct estimation of total QALYs]	[direct estimation of total QALYs]	[direct estimation of total QALYs]	32,800–1,169,600	0.36
Smith*[12]	Heart failure/aortic valve replacement in patients at high risk for operative complications: transcatheter vs. surgical procedure	All-cause mortality at 1-year follow-up	No significant difference at 1 year, but increased survival at 30 days	0	0	27,233–153,187	27,233–153,187	0.11

Publication	Condition: Treatment and Control Procedure	Outcome	Gain in Effect (intervention vs. control procedure)	Lives Saved	QALYs Gained from Lives Saved	QALYs Gained from Greater Quality of Life	Total QALYs Gained	Average QALY Gain per Patient
Altman[24]	Pelvic organ prolapse: Mesh repair vs. vaginal wall suture	Composite success indicator based on clinical indicator (prolapse or no prolapse) and subjective absence of symptoms	Success rate at 1 year increased by 15.6%–37%	n/a	n/a	44,460–105,450	44,460–105,450	0.25
Goss[25]	Chemoprevention for breast cancer in women at higher risk: Exemestane vs. double placebo	Incidence of invasive breast cancer detected by mammography over 3 years	Disease reduction: 65%	2,302–3,947	35,455–60,781	10,674–18,299	46,130–79,080	1.43
Sterling[26]	Latent tuberculosis: 3 months rifapentine + isoniazid with direct observation vs. 9 months self-administered isoniazid	Confirmed tuberculosis diagnosis	13% greater effect by increasing adherence to treatment	71	2,598	28,600–57,200	31,198–59,798	0.06
Guiliano[27]	Prevention of HPV-related lesions and cancers in males: Quadrivalent HPV vaccine vs. placebo	Incidence of lesions	(assuming 100% vaccination rate)					
	Lesions (genital warts)		60% reduction in lesions[27]	n/a	n/a	486–11,509	486–11,509	.02

Publication	Condition: Treatment and Control Procedure	Outcome	Gain in Effect (intervention vs. control procedure)	Lives Saved	QALYs Gained from Lives Saved	QALYs Gained from Greater Quality of Life	Total QALYs Gained	Average QALY Gain per Patient
							17,799–22,938	
	All HPV-related cancers (penile, anal, and oropharyngeal)		60% reduction in disease, assuming 100% cancer prevention if a lesion is averted[28]	1,110–1,380	11,655–14,490	6,144–8,448	Total 18,285–33,997	2.14
Cohen*[13]	Heart failure: Percutaneous coronary intervention (PCI) with paclitaxel-eluting stents vs. bypass surgery (CABG)	Score on disease-specific questionnaire	Gain in quality of life at 1 month (QoL + 0.007), same outcome at 6 and 12 months.	n/a	n/a	5,600–7,000	5,600–7,000	0.01
Ross[16]	Turner's syndrome: Hormonal therapy (growth hormone ± estrogen) vs. placebo	Adult height	Height gain: 2–5 cm, or gain .22–.49 in height standard deviation score	n/a	n/a	2,395–7,184	2,395–7,184	2.36
Louie[29]	*Clostridium difficile* infection: Fidaxomicin vs. vancomycin	Recurrence averted (secondary outcome)	9.9% reduction in recurrence for patients ≥ 65 years old[29]	16–507	171–6,993	43–429	214–7422	0.16
Scheinberg[15]	Immunotherapy for acquired aplastic anemia: Horse vs. rabbit anti-thymocyte globulin	Hematologic response rate	Increase in remission by 31%; also, survival at 3 years increased by 20%	30–60	450–900	465–930	915–1830	3.05
Boeckxstaens[30]	Idiopathic achalasia: Pneumatic dilation vs. laparoscopic Heller's myotomy	Therapeutic success at 1 year (Eckardt score <3)	Not significant	n/a	n/a	n/a	n/a	n/a

Publication	Condition: Treatment and Control Procedure	Outcome	Gain in Effect (intervention vs. control procedure)	Lives Saved	QALYs Gained from Lives Saved	QALYs Gained from Greater Quality of Life	Total QALYs Gained	Average QALY Gain per Patient
Feldman[31]	Mitral regurgitation: Percutaneous repair vs. surgery	Efficacy (no death or need for surgery or recurrence); safety (adverse events at 30 days)	Lower efficacy for the intervention	n/a	n/a	n/a	n/a	n/a
Felker [32]	Acute decompensated heart failure: Diuretic regimens (time x dose)	Composite of self-reported well-being and creatinine level	Not significant	n/a	n/a	n/a	n/a	n/a
Gerstein*[11]	Type 2 diabetes: Intensive therapy vs. standard therapy	Composite measure of nonfatal myocardial infarctions and strokes, and deaths from cardiovascular causes	Not significant and increased mortality at 5 years for intervention group	n/a	n/a	n/a	n/a	n/a
Goldhaber[33]	Thromboprophylaxis in high-risk surgical patients: Apixaban orally or enoxaparin injected	Death at 30 days related to complications; bleeding as primary safety outcome	Not significant	n/a	n/a	n/a	n/a	n/a

Publication	Condition: Treatment and Control Procedure	Outcome	Gain in Effect (intervention vs. control procedure)	Lives Saved	QALYs Gained from Lives Saved	QALYs Gained from Greater Quality of Life	Total QALYs Gained	Average QALY Gain per Patient
Madhi [34]	Prophylaxis against tuberculosis in HIV-exposed infant in South Africa: pre-exposure Isoniazid prophylaxis vs. placebo	Time to disease or death	Not significant	n/a	n/a	n/a	n/a	n/a
Nguyen-Khac[35]	Severe acute alcoholic hepatitis: N-acetylcysteine infusion and oral prednisolone vs. prednisolone alone	Survival at 6 months (i.e., time to death or liver transplant)	Not significant	n/a	n/a	n/a	n/a	n/a

NOTES: Studies are ordered by decreasing gains in total quality-adjusted life years (QALYs); interventions that had no significant effect are listed in alphabetical order at the end of the table.

Estimates in QALY gain are given as lower and upper bound values whenever possible. Average QALY gain per patient was calculated by dividing the average value of the total QALY gain by the mean value for the number of cases.

* Indicates articles describing a secondary analysis of a study; n/a, not applicable based on the criterion that there was no significant gain in effect between intervention and control procedure; HR, hazard ratio.

Only the first author's name of each study is cited here; see references for full citations.

Appendix

The Importance of Published Intervention Studies

Contents

METHODS

Abstraction Tool

Data from each of the 20 studies included in the sample were abstracted using the following grid:

Title
First Author
Volume (issue)
Pages
Date
Institution
Funding
Study Design
Intervention
Primary Outcome
Secondary outcome
Setting
Eligibility
Exclusion
Sample size
Group assignment
Stratification
Study duration
Statistical analysis
Effect of the Intervention
Burden of Disease
Prevalence
Mortality
documented in article?
Information on Quality of Life
documented in article?
Rationale for the Study
documented in introduction?

Formulas Used to Estimate Impact

Lives saved from applying the intervention versus the alternative

$\Delta(\text{Lives saved}) = \text{Deaths}_{ALT} - \text{Deaths}_{X}$

$= \text{Cases} \times (\text{Mortality}_{ALT} - \text{Mortality}_{UNTREATED}) - \text{Cases} \times (\text{Mortality}_{X} - \text{Mortality}_{UNTREATED})$

$= \text{Cases} \times (\text{Mortality}_{ALT} - \text{Mortality}_{X})$

with

Cases = incidence rate x (2011 U.S. population for the age group) if the number was not directly available,

$\text{Mortality}_{UNTREATED}$ = mortality rate if patient is untreated,

Mortality_{ALT} = mortality rate if the control procedure is applied,

and $Mortality_X$ = mortality rate if the intervention is applied.

Cases averted from applying the intervention versus the alternative

$$\Delta(\text{Cases averted}) = \text{Cases} \times (\text{Effectiveness}_X - \text{Effectiveness}_{ALT})$$

with $Effectiveness_X$ = change in the outcome measured if the intervention is applied
and $Effectiveness_{ALT}$ = change in the outcome measured if the control is applied.

QALYs gain from applying the intervention versus the control

$$\Delta QALY = \Delta QALY(\text{Lives saved}) + \Delta QALY(\text{Cases averted})$$

with

$$\Delta QALY(\text{Lives saved}) = \Delta(\text{Lives saved}) \times LE_{Treated} \times QOL_{Treated}$$

and

$\Delta QALY(\text{Cases averted}) = \text{Cases} \times LE_{Treated} \times [\text{Effectiveness}_X \times (QOL_{Treated\ with\ X} - QOL_{Diseased}) - \text{Effectiveness}_{ALT} \times (QOL_{Treated\ with\ ALT} - QOL_{Diseased})]$ if X and Alt lead to different health states (ex kidney transplant vs. dialysis)

$LE_{Treated}$: life expectancy for a patient developing the condition at the average age observed in the study sample.
$QOL_{Diseased}$: Quality of Life coefficient if the condition is untreated.
$QOL_{Treated}$: Quality of Life coefficient if the patient is treated.
$QOL_{Treated\ with\ X}$: Quality of Life coefficient for a patient treated with the intervention.
$QOL_{Treated\ with\ ALT}$: Quality of Life coefficient for a patient treated with the control procedure.

To account for uncertainty, we calculated point estimates using the lower and upper bound values collected for each variable.

TABLE A-1 Articles Reporting an Intervention Excluded from the Sample, and Reason for the Exclusion

Publication	Title	Condition	Study Design	Intervention	Exclusion
Arora[1]	*Outcomes of Treatment for Hepatitis C Virus Infection by Primary Care Providers*	Hepatitis C virus infection	Observational	Community-based health care centers vs. academic center	System level
Bonow[2]	*Myocardial Viability and Survival in Ischemic Left Ventricular Dysfunction*	Heart failure	RCT	Medical therapy alone or combined with bypass	Safety
Huskins[3]	*Intervention to Reduce Transmission of Resistant Bacteria in Intensive Care*	Nocosomial infection	RCT	Expanded barrier/surveillance	System level
Rosenheck[4]	*Long-Acting Risperidone and Oral Antipsychotics in Unstable Schizophrenia*	Schizophrenia	RCT	Risperidone vs. oral antipsychotic	Mental health

NOTES: RCT, random controlled trial.

Only the first author's name of each study is cited here; see references for full citations.

TABLE A-2 Articles Reporting an Intervention Not Selected by the Random Draw

Publication	Title	Condition	Study Design	Intervention
Adzick[5]	*A Randomized Trial of Prenatal versus Postnatal Repair of Myelomeningocele*	Spina bifida	RCT	Prenatal vs. postnatal intervention
Appel[6]	*Comparative Effectiveness of Weight-Loss Interventions in Clinical Practice*	Obesity	RCT	Intervention vs. self-support
Aufderheide[7]	*A Trial of an Impedance Threshold Device in Out-of-Hospital Cardiac Arrest*	Heart failure	RCT	Active threshold device vs. sham
Avidan[8]	*Prevention of Intraoperative Awareness in a High-Risk Surgical Population*	Surgery, quality	RCT	2 methods for monitoring awareness during surgery
Bacon[9]	*Boceprevir for Previously Treated Chronic HCV Genotype 1 Infection*	HCV	RCT	Peginterferon and ribavirin ± boceprevir
Bednarek[10]	*Immediate versus Delayed IUD Insertion after Uterine Aspiration*	Birth control	RCT	Timing of intrauterine device (IUD) insertion
Busse[11]	*Randomized Trial of Omalizumab (Anti-IgE) for Asthma in Inner-City Children*	Asthma	RCT	Omalizumab vs. placebo
Chimowitz[12]	*Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis*	Stroke	RCT	Stent vs. medical therapy
Coleman[13]	*Breast-Cancer Adjuvant Therapy with Zoledronic Acid*	Breast cancer	RCT	Chemotherapy alone or combined with zoledronic
Connolly[14]	*Apixaban in Patients with Atrial Fibrillation*	Stroke prevention	RCT	Apixaban vs. aspirin
Conroy[15]	*FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer*	Pancreatic cancer	RCT	4-drug regimen vs. 5-drug regimen with germcitabine
Cypel[16]	*Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation*	Organ transplant	Observational	Transplant perfused or not
de Bono[17]	*Abiraterone and Increased Survival in Metastatic Prostate Cancer*	Prostate cancer	RCT	Abiteranone vs. placebo
Duncan[18]	*Body-Weight–Supported Treadmill Rehabilitation after Stroke*	Stroke	RCT	Locomotor training (two different initiation times) vs. home exercise
Granger[19]	*Apixaban versus Warfarin in Patients with Atrial Fibrillation*	Atrial fibrillation	RCT	Apixaban vs. warfarin
INIS Collaborative Group[20]	*Treatment of Neonatal Sepsis with Intravenous Immune Globulin*	Infant health	RCT	Immune globulin vs. placebo

Publication	Title	Condition	Study Design	Intervention
Jacobson[21]	*Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection*	HCV infection	RCT	Usual drug regimen or combination with telaprevir
Jain[22]	*Veterans Affairs Initiative to Prevent Methicillin-Resistant Staphylococcus aureus Infections*	Nocosomial infection	Observational	Expanded barrier/surveillance
Kastrati[23]	*Abciximab and Heparin versus Bivalirudin for Non–ST-Elevation Myocardial Infarction*	Myocardial infarction	RCT	Drug comparisons
Löwenberg[24]	*Cytarabine Dose for Acute Myeloid Leukemia*	Leukemia	RCT	Dose comparison
Martinson[25]	*New Regimens to Prevent Tuberculosis in Adults with HIV Infection*	Co-infection with TB and HIV	RCT	Comparison of 4 drug regimens
Mathurin[26]	*Early Liver Transplantation for Severe Alcoholic Hepatitis*	Alcoholic hepatitis	Observational	Early transplantation (at 2 months) vs. usual timing (at 6 months)
McCormack[27]	*Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis*	Cystic lung disease	RCT	Sirolimus vs. placebo
Mintz-Hittner[28]	*Efficacy of Intravitreal Bevacizumab for Stage 3+ Retinopathy of Prematurity*	Preterm infant	RCT	Intravitreal bevacizumab vs. laser therapy
NLST[29]	*Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening*	Lung cancer	RCT	Imaging method: 3 CT scans vs. 1 X-ray per year
O'Connor[30]	*Effect of Nesiritide in Patients with Acute Decompensated Heart Failure*	Heart failure	RCT	Nesiritide vs. placebo
O'Shaughnessy[31]	*Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer*	Breast cancer	RCT	Gemcitabine and carboplatin ± iniparib
Palefsky[32]	*HPV Vaccine against Anal HPV Infection and Anal Intraepithelial Neoplasia*	HPV	RCT	Quadrivalent HPV vaccine vs. placebo
Pimentel[33]	*Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation*	Irritable bowel syndrome	RCT	Rifaxin vs. placebo
Poordad[34]	*Boceprevir for Untreated Chronic HCV Genotype 1 Infection*	HCV	RCT	Peginterferon and ribavirin ± boceprevir
Reich[35]	*A 52-Week Trial Comparing Briakinumab with Methotrexate in Patients with Psoriasis*	Psoriasis	RCT	Briakinumab vs. methotrexate
Sherman[36]	*Response-Guided Telaprevir Combination Treatment for Hepatitis C Virus Infection*	HCV	RCT	Treatment duration (+4 weeks vs. +28 weeks)

Publication	Title	Condition	Study Design	Intervention
Stiell[37]	*Early versus Later Rhythm Analysis in Patients with Out-of-Hospital Cardiac Arrest*	Heart failure	RCT	Length of CPR and timing of rhythm analysis
Thera[38]	*A Field Trial to Assess a Blood-Stage Malaria Vaccine*	Malaria	Observational	Malaria vaccine vs. control vaccine (Rabies)
Vesikari[39]	*Oil-in-Water Emulsion Adjuvant with Influenza Vaccine in Young Children*	Flu prevention	RCT	Influenza vaccine, influenza vaccine with adjuvant, or control vaccine
Viviani[40]	*ABVD versus BEACOPP for Hodgkin's Lymphoma When High-Dose Salvage Is Planned*	Hodgkin's lymphoma	RCT	Chemotherapy comparison
Wadden[41]	*A Two-Year Randomized Trial of Obesity Treatment in Primary Care Practice*	Obesity	RCT	Counseling vs. usual care
Zannad[42]	*Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms*	Heart failure	RCT	Eplerenone vs. placebo
Zeiger[43]	*Daily or Intermittent Budesonide in Preschool Children with Recurrent Wheezing*	Asthma prevention	RCT	Frequency of treatment
Zeuzem[44]	*Telaprevir for Retreatment of HCV Infection*	HCV infection	RCT	Usual treatment alone or combined with telaprevir

NOTES: RCT, random controlled trial; HCV, hepatitis C virus; IUD, intrauterine device; HIV, human immunodeficiency virus; HPV, human papillomavirus; TB, tuberculosis bacillus.

Only the first author’s name of each study is cited here; see references for full citations.

TABLE A-3 Information and Sources on Interventions, Disease Burden, and Expected Impact of the Intervention (Lives Saved, Cases Averted, and QALY Gains)

Publication	Condition, Intervention, and Control Procedure	Average Age in Study Sample	Life Expectancy,[45] Adjusted for Condition	Disease Burden: Morbidity	Disease Burden: Mortality	Individual QALY Gain (improved quality of life, case averted, life saved)	Gain in Effect (intervention vs. control procedure)
Velazquez[46]	Left ventricular dysfunction: Bypass surgery (CABG) with medical therapy vs. medical therapy alone	60 years old	10–23 years	5.8 million cases of heart failure per year in U.S.[46] 849,000 patients receiving a CABG or PCI in 2010[33] → 849,000 cases	3-year mortality rate= 25%[46] → 212,250 deaths	0.1 QALY per year if survival at 10 years[47] [QoL= 0.8 if medically treated QoL= 0.9 with CABG if survival at 10 years[47]] 17.28 QALY if death averted [based on QoL=0.87 at ages 60–64; QoL =0.84 at ages 65–74; QoL =0.78 at ages 75–83[48]]	Reduced mortality with CABG HR = 0.86 [.72, 1.04] → risk reduction = 0–6%
De Boer[49]	Renal function in type 1 diabetes: intensive or conventional diabetes therapy	27 years old	40 years [10 years loss to diabetes type 1[50]]	Type 1 diabetes = 5% all diabetes (25.8 million)[51] → 1.29 million cases	13 times increase in mortality increased 13x upon ESDR (from 3–5% to 40–60%)[49]	0.25 QALY gain per year per case averted 30 QALY gained per death averted [based on QoL for kidney failure =0.5 vs. QoL for managed diabetes: 0.75[47, 52]]	Risk reduction 50% [18%, 69%] for end-stage

Publication	Condition, Intervention, and Control Procedure	Average Age in Study Sample	Life Expectancy,[45] Adjusted for Condition	Disease Burden: Morbidity	Disease Burden: Mortality	Individual QALY Gain (improved quality of life, case averted, life saved)	Gain in Effect (intervention vs. control procedure)
West[53]	Smoking cessation: Cytisine vs. placebo	48 years old	32 years	52.4 % smokers who attempted quitting = 23.7 million[53 54]	443,000 premature deaths related to smoking in the U.S.[54]	.25–1.4 QALY gained per person who quit smoking [based on QALY loss =.044 for smoking per year[48] (accounts for mortality and morbidity) and average loss of 3 months of life expectancy over 45 years (= .25 years) for a smoker 30+ years)[54]]	6% increase in smoking cessation at 12 months
Villareal[55]	Obesity in older adults: weight loss, physical activity, or both	70 years old	8–15 years [0–7 years lost to obesity[56]]	20–21% adult >70 years are obese[55, 57] → 1.64–1.72 million cases	13,500–42,500 deaths in 2000 [53,754–170,064 deaths related to BMI>30; with 25% among > 70 years[58]]	0.02–0.68 QALY [0.17 QALY gain by loss of 1 BMI unit[59]; 0.02–0.1 QALY gain for changing from obesity Class II to Class I[60]]	Average loss of 4 BMI points resulting in obesity class change [Average BMI at baseline = 37; average BMI after intervention = 33]

Publication	Condition, Intervention, and Control Procedure	Average Age in Study Sample	Life Expectancy,[45] Adjusted for Condition	Disease Burden: Morbidity	Disease Burden: Mortality	Individual QALY Gain (improved quality of life, case averted, life saved)	Gain in Effect (intervention vs. control procedure)
Smith*[61]	Heart failure/aortic valve replacement in patients at high risk for operative complications: transcatheter vs. surgical procedure	83 years old	6 years with replacement; 2–3 years if no intervention[62]	4–5% people aged >75 years[62] → 756,000–946,000 cases	Mortality: 50% at 2 years without replacement; 30% after replacement[61] → 151,000–189,000 lives saved with either procedure	0.02–0.09 QALY per year[63]	Higher survival at 30 days, no significant difference at 1 year
Altman[64]	Pelvic organ prolapse: Mesh repair vs. vaginal wall suture	65 years old	19 years	300,000 surgeries per year in the U.S.[64]	n/a	0.05 QALY per year per case[65]	Success rate at 1 year: increased by 15.6%–37%

Publication	Condition, Intervention, and Control Procedure	Average Age in Study Sample	Life Expectancy,[45] Adjusted for Condition	Disease Burden: Morbidity	Disease Burden: Mortality	Individual QALY Gain (improved quality of life, case averted, life saved)	Gain in Effect (intervention vs. control procedure)
Goss[66]	Chemoprevention for breast cancer in women at higher risk: exemestane, exemestane + celecoxib, celecoxib, or double placebo (assuming treatment is received for 5 years and risk reduction is applicable to the treatment period only)	62 years old	20 years	1.4–2.4 million women at higher risk of breast cancer[67] → 32,200–55,200 invasive cancers over 5 years [based on the median 5-year breast cancer risk of the sample given by Gail risk score: 2.3%]	5-year survival rate for ER-positive breast cancer: 89%[68] → 3,542–6,072 deaths over 5 years	15.4 QALY gained per live saved [4 years at QoL= 0.68 + 16 years with QoL =0.79 at ages 66+ accounting for chemoprevention side effects (QoL reduced by 0.05)[48]] 0.51 QALY per case averted [QoL increased from 0.68 to 0.87 over 4 years; side effects of chemoprevention for 5 years: QoL reduced by 0.05[47]]	Disease reduction: 65%
Sterling[69]	Latent TB: 3 months rifapentine + isoniazid with direct observation vs. 9 months self-administered isoniazid	35 years old	45 years	11 million cases of latent TB in U.S.: 5–10% develop TB with about half within 2 years after infection[70]	547 deaths in 2009[70]	0.4 per case averted for 3 months[47]	13% more effect by increasing adherence
Guiliano[71]	Prevention of genital lesions: HPV vaccination of young males (assuming 100% vaccination rate)	20 years old	59 years	180,000–640,000 male cases per year[72] with 90% caused by HPV[73] → 162,000–576,000 cases	n/a	0.005–0.032 QALY [based on QoL 0.87–0.98 for 3 months[73–75]]	60% reduction in lesions[71]

Publication	Condition, Intervention, and Control Procedure	Average Age in Study Sample	Life Expectancy,[45] Adjusted for Condition	Disease Burden: Morbidity	Disease Burden: Mortality	Individual QALY Gain (improved quality of life, case averted, life saved)	Gain in Effect (intervention vs. control procedure)
	Prevention of 11 HPV-related cancers (penile, anal, and oropharyngeal): HPV vaccination of young males (assuming 100% vaccination rate)	70 years old at cancer incidence	15 years	8,000–11,000 cases among U.S. males per year[72,76]	1,850–2,300 deaths among U.S. males per year[72,76]	1.28 QALY per cancer averted [based on QoL =0.68 for 4 years[73]] + 10.5 QALY per death averted [based on QoL=0.68 for 4 years (ages 70–74) and QoL =0.78 at ages 75–85[48]]	60% reduction in disease, assuming that lesion reduction results in 100% cancer reduction[73]
Cohen*[77]	Heart failure: percutaneous coronary intervention (PCI) with paclitaxel-eluting stents vs. bypass surgery (CABG)	65 years old	19 years	1 million procedures per year[78] Repeat vascularization increased 20% with PCI[78] → gain in quality of life applied to 80–100% patients	No overall difference between the two procedures[78]	0.007 QALY [QoL increased by 0.08 for 1 month with PCI vs. CABG[77]] [we assumed zero QALY gained for repeat procedures =20% cases]	Gain in quality of life at 1 month (QoL +0.007), same outcome at 6 and 12 months
Ross[79]	Turner's syndrome: Hormonal therapy (growth hormone ± estrogen) vs. placebo	8 years old	59 years (accounts for life expectancy shorter by 10 years[80])	1 in 2,000 live births in U.S.[79] → ~ 2000 births per year	n/a	0.02–0.06 QALY per year (our assumption is based on height gain; QoL was reported to be normal to modestly increased on height gain[81–83])	Height gain: 2–5 cm, or gain .22–.49 height SDS

Publication	Condition, Intervention, and Control Procedure	Average Age in Study Sample	Life Expectancy,[45] Adjusted for Condition	Disease Burden: Morbidity	Disease Burden: Mortality	Individual QALY Gain (improved quality of life, case averted, life saved)	Gain in Effect (intervention vs. control procedure)
Louie[84]	*Clostridium difficile* infection: Fidaxomicin vs. vancomycin	60 years old	19–23 years	35,000–350,000 cases in U.S. (50%: ≥ 65 years)[85] 25% recurrence overall[84] → 4,375–43,750 recurrent episodes for patients ≥ 65 years old	Mortality 3.7–11.7%[85,86] → 162–5,119 deaths for patients ≥ 65 years old	0.04–0.319 QALY per case averted[87,88] 10.7–13.8 QALY per death averted [QoL = 0.84 at ages 65–74, QoL= 0.78 at ages 75–83[48]]	9.9% reduction in recurrence for patients ≥ 65 years old[84]
Scheinberg[89]	Immunotherapy for acquired aplastic anemia: Horse vs. rabbit antithymocite globulin	34 years old	20 years[90]	300–600 cases per year (1 to 2 cases per million)[91]	If remission: probability survival at 15 years = 50% (mean age = 20 years)[90]	15 QALY gained from death averted 5 QALY gained from remission [based on QoL=0.5 if treated; QoL=0.75 if treated and remission[90]]	Increase in remission by 31% and survival at 3 years increase by 20%
Boeckxstaens[92]	Idiopathic achalasia: Pneumatic dilation vs. laparoscopic Heller's myotomy	45 years old	36 years	Annual incidence of approximately 1/100,000 and prevalence rate of 1/10,000[93]	n/a	n/a	Not significant
Feldman[94]	Mitral regurgitation: Percutaneous repair vs. surgery	66 years old	19 years	2–2.5 million cases in U.S.[95]	3–6%[94] → 60,000–150,000 deaths	n/a	Lower efficacy for the interventions
Felker[96]	Acute decompensated heart failure: Diuretic regimens (time x dose)	66 years old	12 years (based on 7 years lost to heart disease[50])	> 1 million per year in U.S., with 90% receiving diuretic drug[96] → 900,000 cases	20% mortality after discharge[97] → 180,000 deaths	n/a	Not significant

Publication	Condition, Intervention, and Control Procedure	Average Age in Study Sample	Life Expectancy,[45] Adjusted for Condition	Disease Burden: Morbidity	Disease Burden: Mortality	Individual QALY Gain (improved quality of life, case averted, life saved)	Gain in Effect (intervention vs. control procedure)
Gerstein*[98]	Diabetes type 2	62 years old	18 years (5 years lost to diabetes[99])	10.9 million U.S. adults ≥ 65 years[51]	20 per 100,000 diabetic ≥ 65 years[100] → 2,180 deaths	n/a	Not significant and increased mortality at 5 years for intervention group
Goldhaber[101]	Thromboprophylaxis in high-risk surgical patients: apixaban orally or enoxaparin injected	66 years old	19 years high-risk surgical patients	25–50% incidence rate for patients > 40 years undergoing major surgery and patients > 60 years undergoing minor surgery[102]	0.4–1.0% mortality rate for patients > 40 years undergoing major surgery or patients > 60 years undergoing minor surgery[102]	n/a	Not significant
Madhi[103]	Prophylaxis against tuberculosis in HIV-exposed infant in South Africa: preexposure isoniazid prophylaxis vs. placebo	3 months old	14–16 years if HIV infected[104]	1,596 cases per 100,000 HIV-infected infants[103] < 200 infants infected perinatally in U.S. each year	TB is leading death cause in HIV-infected infants (12–18% mortality in group)	n/a	Not significant
Nguyen-Khac[105]	Severe acute alcoholic hepatitis: N-acetylcysteine infusion + oral prednisolone vs. prednisolone alone	52 years old	1–2 years[105,106]	16 million cases of alcoholism in U.S. ; incidence alcoholic hepatitis = 35%[106] → 5 million cases	Age and gender adjusted mortality = 4.4 per 100,000[106] → 220 deaths per year	n/a	Not significant

NOTES: The values reported here were used to estimate the population impacted reported in Table 1 and Figure 2. Lower and upper values were indicated whenever available to account for the uncertainty of the estimates.

* Indicates secondary reports for a study; QALY, quality-adjusted life years; QoL, quality of life; PCI, percutaneous coronary intervention; HR, hazard ratio; ESRD, end-stage renal disease; BMI, body mass index; TB, tuberculosis; HPV, human papillomavirus; SDS, standard deviation score ; HIV, human immunodeficiency virus; HIV, human immunodeficiency virus.

Only the first author's name of each study is cited here; see references for full citations.

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