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The AMA proposal to mandate nicotine reduction in cigarettes: a simulation of the population health impacts

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Abstract

Background. The American Medical Association (AMA) has advocated gradually reducing the nicotine content of cigarettes to decrease smoking prevalence. Some experts have voiced concerns that smokers may "compensate" by smoking more cigarettes or inhaling more deeply. Further, a black market may emerge, perpetuating cigarette availability. Thus, it is unclear whether a federal mandate would result in a net increase or decrease in population health. The purpose of this research is to estimate the long-term health gains or losses that are likely to accrue to the US population if the nicotine content of cigarettes is gradually reduced to trace levels over a 6-year period.

Methods. To estimate health impacts, we created the Tobacco Policy Model, a computer simulation model. The model simulates the US population as they age and change their smoking behavior over time. Secondary data for model parameters were obtained from publicly available sources. Population health impacts were measured as the change in cumulative quality-adjusted life-years (QALYs) in the US population over 50 years.

Results. Following a mandate to reduce nicotine, smoking prevalence is likely to decline from 23% to 5% of the population. Accordingly, a cumulative gain of 157 million QALYs is expected over 50 years.

Conclusions. Despite any mortality increases due to compensatory smoking or the emergence of a black market, implementation of the AMA proposal would likely prevent the addiction of scores of new smokers and result in important gains to the nation's health. This research should prove useful to Congress as they contemplate giving the FDA the authority to regulate tobacco.

Keywords: Smoking; Cigarette; Population

Background

A number of approaches have been tried to reduce tobacco use. Provocative anti-tobacco messages cross our TV screens daily, tobacco excise taxes have inched upward, and many physicians regularly counsel their patients to quit smoking. Despite all of these efforts, approximately one-quarter of the US population still smokes [1]. Frustrated with the lack of progress, opinion leaders and policy makers have begun to seriously discuss the value of a more drastic measure—reducing the main ingredient in cigarettes that induces people to smoke: nicotine [2–7].

AMA proposal to mandate nicotine reductions

The Minnesota delegation of the American Medical Association (AMA) first proposed that the AMA "develop and support legislation that would require tobacco companies to reduce the nicotine content in tobacco products sold in the United States by an appropriate, graduated, incremental annual reduction process so that tobacco products would be nicotine-free in six years…" [6] This proposal was based, in part, on a *New England Journal of Medicine* commentary published in 1994 [7]. The AMA's Council on Scientific Affairs then took interest in the issue. At the 147th annual meeting in June of 1998, the AMA House of Delegates voted to "reaffirm…its position that the FDA (has)…the authority to regulate tobacco." The emerging policy statement vowed that the AMA would "encoura-

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ge. . .research on how tobacco products might be modified to facilitate cessation of use, including elimination of nicotine. . .(and). . . encourage the FDA to assert its authority over the manufacture of tobacco products to reduce their addictive potential at the earliest practical time, with the goal for implementation within five to 10 years.'' The report, endorsed by the AMA House of Delegates, also emphasized the importance of addressing issues such as the need for treatment to accompany such an approach, education of health professionals and tobacco users, and control over smuggling.

Hazards of smoking

The AMA's proposal to reduce the nicotine content of cigarettes is, of course, intended to reduce smoking, the single leading preventable cause of death in the United States [8]. Tobacco use causes more fatalities each year than AIDS, alcohol, cocaine, heroin, homicide, suicide, motor vehicle crashes, and fires combined [9]. On average, smokers die more than 6 years before non-smokers [10], from causes such as cardiovascular disease, cancer, and emphysema. In addition, they experience a host of other health problems ranging from poor wound healing [11] to impotence [12].

While the drug nicotine is the primary reason that people smoke, it is not the primary causal agent of most of the health problems associated with smoking. To be sure, nicotine does have some negative impact on cardiovascular health [13] and fetal pulmonary development [14–16], and it may be associated with sudden infant death syndrome [17–19]. On the other hand, nicotine may be protective against certain diseases such as ulcerative colitis, Alzheimer's, and Parkinson's [20]. Regardless, it is not the nicotine in cigarettes, but rather the toxins—the carcinogens, teratogens, and carbon monoxide—that cause most smoking-induced diseases. It is, however, the compulsion for nicotine that induces smokers to expose themselves to these toxins. The result is disease and premature death.

The addictive potential of nicotine

Based on the criteria of the World Health Organization [21], the U.S. Surgeon General [22], and the American Psychiatric Association [23], nicotine is a dependence-producing drug. Further, tobacco industry documents show that the industry developed and marketed its products on the assumption that nicotine was addictive and with intent to ensure that cigarettes provided sufficient levels of nicotine to sustain addiction [24–26]. In a memo to his industry colleagues, Addison Yeaman, General Counsel and Vice President of Brown and Williamson wrote ''Moreover, nicotine is addictive. We are, then, in the business of selling nicotine, an addictive drug. . .'' [27].

Reducing nicotine is technologically feasible

It was insider information on the industry's deliberate manipulation of the nicotine levels in cigarettes that served as the impetus for the FDA's assertion that they have the authority to regulate tobacco [28–31]. Considerable evidence is available that the nicotine content of cigarettes can be readily altered. For example, the nicotine content of tobacco plants varies; to reduce nicotine levels, commonly used nicotine-rich varieties, such as *Nicotiana rustica*, can simply be replaced with lower-nicotine varieties [32] and new plant varieties can be created through genetic manipulation. Further, because tobacco leaves found near the top of the plant contain higher concentrations of nicotine, substituting leaves found lower on the plant will reduce the nicotine content of cigarettes. Nicotine can also be removed from tobacco via supercritical extraction technology, a high-pressure carbon dioxide process similar to the process used to decaffeinate coffee. Finally, perhaps the best evidence that manufacturing a cigarette with trace levels of nicotine is feasible is that it has already been done. Phillip Morris introduced the brand Next, marketed as a ''denicotinized'' cigarette, in the early 1990s [33].

The risk of compensatory smoking

Faced with reduced levels of nicotine in their cigarettes, many smokers will quit. However, scientific evidence with low-yield cigarettes indicates that those who continue to smoke may compensate for the loss of nicotine by smoking more cigarettes [34] or smoking each cigarette to a shorter butt length [35,36]. In addition, they may change the way they smoke by, for example, blocking the invisible filter vents in cigarettes with their lips or fingers, impeding the dilution of smoke and increasing the concentration of nicotine in each puff [37], or by increasing their puff volume [35,36,38–40]. With these methods of ''compensatory smoking,'' smokers can effectively titrate the dose of nicotine they receive [41].

Unfortunately, compensatory smoking may increase risks to smokers. Deeper inhalation, for example, may result in an increased risk of squamous cell carcinoma due to the increased exposure of peripheral lung tissues to additional carcinogens [42]. The risk of premature mortality has also been shown to increase with the number of cigarettes smoked per day [43]. Because compensatory smoking may lead to greater health problems in smokers, it thus has the potential to partially defeat the intent of a federal mandate, which is to improve population health.

Compounding our uncertainty about the possible impact of reducing nicotine levels in cigarettes, the above evidence on the likelihood, nature, and danger of compensatory smoking is obtained from research on reduced-yield cigarettes not reduced nicotine content cigarettes.

The risk of an emerging black market

Smuggling, both interstate and international, currently accounts for approximately 8% of cigarette consumption in the US [44]. International smuggling of cigarettes into the US will surely increase with the federal mandate contemplated here. In response to concerns about smuggling, advocates of the nicotine reduction policy suggest that law enforcement efforts can be intensified, stricter penalties imposed, and cigarette packaging regulated so that legal and illegal cigarettes can be distinguished by law enforcement authorities [45]. Of course advocates recognize that even with these efforts, some level of "leakage" will always occur. It will be impossible to completely curtail the black market.

Not only will the black market provide continuing access to nicotine, thus perpetuating some smoking, cigarettes purchased on the black market may also be riskier. Chinese counterfeit versions of Regal and Silk Cut cigarettes, for example, are thought to contain banned chemicals and higher levels of tar than the originals [46]. Cigarettes produced to meet the demand of a black market will circumvent current FDA labeling policies that require packages to display FTC-measured yields of tar and nicotine and messages about harm. Further, just as illicit street drugs may contain any amount of the drug, impurities, or different chemicals altogether, black market cigarettes might have greater or lesser amounts of nicotine and tar than cigarettes currently consumed in the US.

Given these concerns, many of which were discussed in the AMA proposal itself, the wisdom of reducing nicotine in cigarettes is unclear. In particular, there are a number of factors that may not be readily controlled by a policy focused on nicotine removal. For example, the increased risks to smokers who are likely to "compensate" when smoking low-nicotine cigarettes, combined with any health risks associated with purchasing cigarettes on the black market, may offset any health gains from reduced tobacco use. It may be that factors like these cannot be readily influenced by policy and thus the unintended and potentially deadly consequences must be anticipated in policy making. Thus, to aid policy decisions, the purpose of this research is to combine all of these factors into a single model to estimate the health impacts to the US population if the nicotine content of cigarettes is reduced gradually over a period of 6 years.

Methods

To estimate the anticipated population health impacts from reducing nicotine in cigarettes, we used the Tobacco Policy Model. The model is described in more detail elsewhere [47,48]; thus, it is described only briefly here.

The tobacco policy model

We developed the Tobacco Policy Model, a flexible computer simulation model, to calculate the public health gains or losses from any change in tobacco use. The model has been calibrated to ensure accuracy.

To begin the present simulation, we initialized the model with the number of people in the US population in the year 2003 [49], and divided the population into cohorts according to age, gender, and smoking status (current, former, or never smoker) [1,50,51]. We then used the model to simulate annual transitions such as birth, death, aging, net migration, and changes in smoking behavior in the US population over 50 years. Transition probabilities vary by age, gender, smoking status, and year.

Three types of smoking behavior change are simulated: initiation (the transition from being a never smoker to being a current smoker), cessation (current to former smoker), and relapse (former to current smoker). Data used to estimate annual behavior change probabilities were obtained from various sources [50–53]. Using statistical regression, we fit separate hazard functions for each type of smoking behavior change by age, gender, and interaction terms.

In the Tobacco Policy Model, gains or losses in health are measured with quality-adjusted life-years (QALYs). The QALY measure, recommended by the US Task Force on Cost-Effectiveness in Health and Medicine [54], combines improvements in length of life and health-related quality of life into a single measure. For example, 10 years of life at 85% quality would result in 8.5 QALYs. We estimated mortality hazard functions using mortality data for each gender [49,55,56].

Quality of life data for current, former, and never smokers of various ages and genders were obtained from the Quality of Well Being scale [57]. Current smokers reported lower health-related quality of life than former smokers who reported lower health-related quality of life than never smokers. Differences in quality of life reported by the three groups are likely due to the health problems associated with smoking. Further, it is likely that former smokers factored in the reduced health-related quality of life associated with any craving or nicotine withdrawal symptoms (anxiety, depression, etc.) [58] when responding to the survey.

Model assumptions

We evaluated the implications of a federal mandate requiring that tobacco manufacturers reduce the nicotine content of cigarettes gradually and incrementally over a 6-year period until only trace and non-addictive levels of nicotine remain. Although not specified here, the final threshold might be 0.17 mg as recommended by Benowitz and Henningfield [7]. This hypothetical decline in nicotine levels is depicted at the top of Fig. 1.

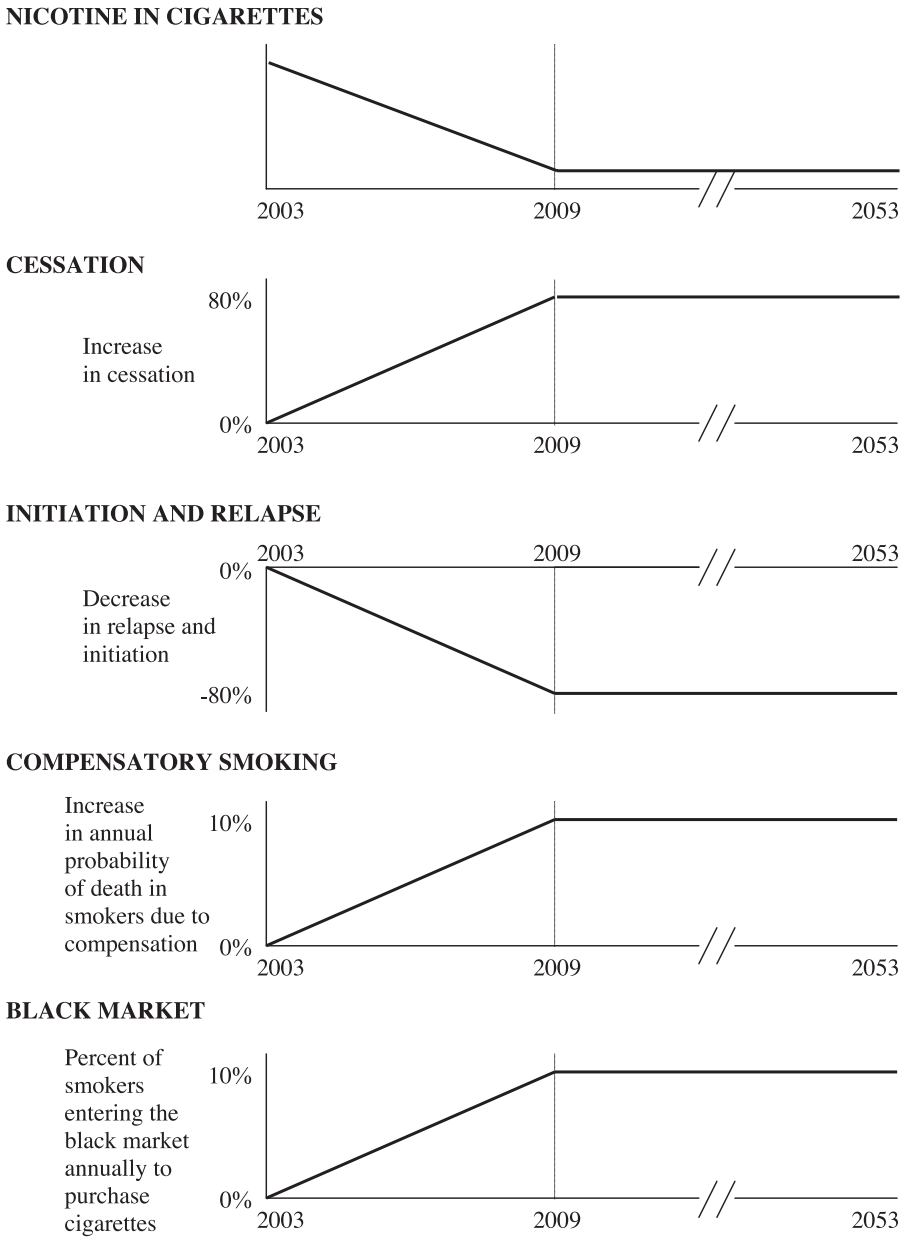

Fig. 1. Model assumptions.

Also depicted in Fig. 1 are the four consequences that we would expect to follow from reducing the nicotine content of cigarettes. First, faced with reduced levels of nicotine, current smokers will be more likely to quit smoking. We assumed that the probability of cessation, which varies by age and gender, would increase in a linear fashion in direct proportion to the level of nicotine in cigarettes. Second, as nicotine is reduced, former smokers may be less likely to relapse and never smokers may be less likely to start smoking. To simulate this, we decreased the annual probability of initiation and relapse, which also vary by age and gender, over the 6-year period.

To understand how we made the changes described above, first note that the maximum hypothetical probability of cessation is 1.0 and the minimum probability of initiation and relapse is 0. However, it seems implausible that, even with trace levels of nicotine, all smoking would cease and no one would ever start or resume smoking ever again. Thus, to estimate behavior change, we began by calculating the age- and gender-specific differential between the current probability of cessation and 1.0, the current probability of initiation and 0, and the current probability of relapse and 0. We then decreased these differentials, not by 100% (which would reduce the prevalence of smoking to zero immediately), but by 80% at the end of 6 years. For example, we assumed that the annual probability of initiation for 18-year-old males would decrease from 0.1 to 0.02 (calculated as $0.1 - 0.8 \times |0-0.1| = 0.02$) while the probability for 20-year-old males

would decrease from 0.05 to 0.01 (calculated as $0.05 - 0.8 \times |0 - 0.05| = 0.01$) over 6 years. As another example, we assumed the annual probability of cessation for 65-year-old females would increase gradually over 6 years from 0.04 to 0.81 (calculated as $0.04 + 0.8 \times |1 - 0.04| = 0.81$)).

A third consequence that would likely follow any federal mandate is that those who continue smoking, despite decreasing levels of nicotine in their cigarettes, may seek to maintain their exposure to nicotine by smoking more cigarettes per day [34] and/or increasing their puff volume per cigarette [35,36,38–40]. We used data from the National Cancer Institute [34] on the inverse relationship between nicotine levels and cigarettes smoked per day to estimate the likely increase in cigarettes. We also estimated the cigarette-equivalent from increased puff volume and combined the two estimates. We then used data from the Current Population Survey [43] on the relationship between number of cigarettes smoked per day and mortality rates to estimate the increase in mortality that is likely to occur in those who continue to smoke. Using these methods, we estimated that mortality in current smokers may increase by 10% due to compensatory smoking.

A fourth possible consequence of mandating reduced-nicotine cigarettes is that smokers who do not quit may turn to the black market to purchase cigarettes containing nicotine. For the purpose of this paper, we define the black market as all sources of "regular nicotine" cigarettes following a US federal mandate. These sources include foreign-manufactured brands, US brands produced for overseas consumption that are smuggled back into the US, and loose leaf tobacco used to produce "roll-your-own" cigarettes. Note that this definition excludes some of the illegal activity currently considered part of the "black market", notably inter-state smuggling, as this would not be a source of regular nicotine cigarettes after a nationwide mandate. Conversely, our definition includes some activity that is currently lawful, most notably rolling your own cigarettes. Due to this context-specific definition, we were not able to use the available 8% figure [44] as our estimate of the percent of smokers currently purchasing cigarettes in the black market. Further, because evidence of illegal activity is difficult to obtain, we used an indirect method of estimation. First, we obtained data on the total federal excise taxes collected on domestic cigarettes and imported tobacco products [59] and divided this by the federal excise tax per pack [60] to estimate the number of packs on which taxes were collected in a single year. We then subtracted this figure from the larger number of packs consumed in the US annually [61]. We assumed that this difference represented the number of packs currently purchased illegally. We divided this number by the total packs consumed to calculate that 3.6% of packs were purchased on the black market. After rounding, we thus estimated that 4% of smokers currently purchase their cigarettes from the black market. As depicted in Fig. 1, we also assumed that, following the passage of legislation, the percent of current smokers joining their ranks annually would increase linearly up to 10% in 6 years.

Using the baseline parameter estimates described above, we simulated the cohort for 50 years. First, we ran the model assuming no change in policy. Second, we ran the model assuming a federal mandate requiring nicotine to be gradually reduced in cigarettes. For each model run, we estimated the total cumulative QALYs that would be expected to accrue to the entire US population over that period. We then calculated the difference in QALYs produced with two model runs to estimate the change in population health that would be anticipated due to the federal mandate.

Sensitivity analyses

Because there are many uncertainties, it is important to evaluate the sensitivity of results to the assumptions incorporated into the model. For example, while we assumed that smoking behavior would change by 80% in 6 years, this estimate is uncertain. Thus, we also considered degrees of smoking behavior change ranging from 0% to 100%. Also uncertain is the extent to which smokers, deprived of nicotine, will engage in compensatory smoking, increasing their mortality rate. While we assume that mortality would increase by 10%, we consider increases in mortality ranging from 0% to 100%. To perform the two-way sensitivity analysis, for each hypothetical change in behavior (0%, 10%, 20%, . . ., 100%) combined with a change in mortality (0%, 10%, 20%, . . ., 100%), we estimated the gain in QALYs to the US population over 50 years.

In addition to the two-way sensitivity analysis described above, we also performed a pair of one-way sensitivity analyses. In the first, we varied the percent of smokers entering the black market annually from 0% to 50%. In the second, we varied the year in which the policy mandate would take effect from 2003 to 2053. In both cases, we assessed whether model-simulated outcomes differed greatly depending on the variable in question (black market entry or year of implementation) and whether these differences were likely to influence the judged wisdom of a federal mandate.

Results

As shown in Fig. 2, using current rates of initiation, cessation and relapse, simulation results indicate that 23% of the US population are expected to be current smokers in 50 years. However, following a federal mandate requiring the reduction of nicotine in cigarettes, the prevalence of smoking is likely to be substantially lower—5% of the population in 50 years. Virtually all of these smokers are expected to purchase their cigarettes from the black market.

Reducing the prevalence of smoking will result in an increase in both survival and health-related quality of life,

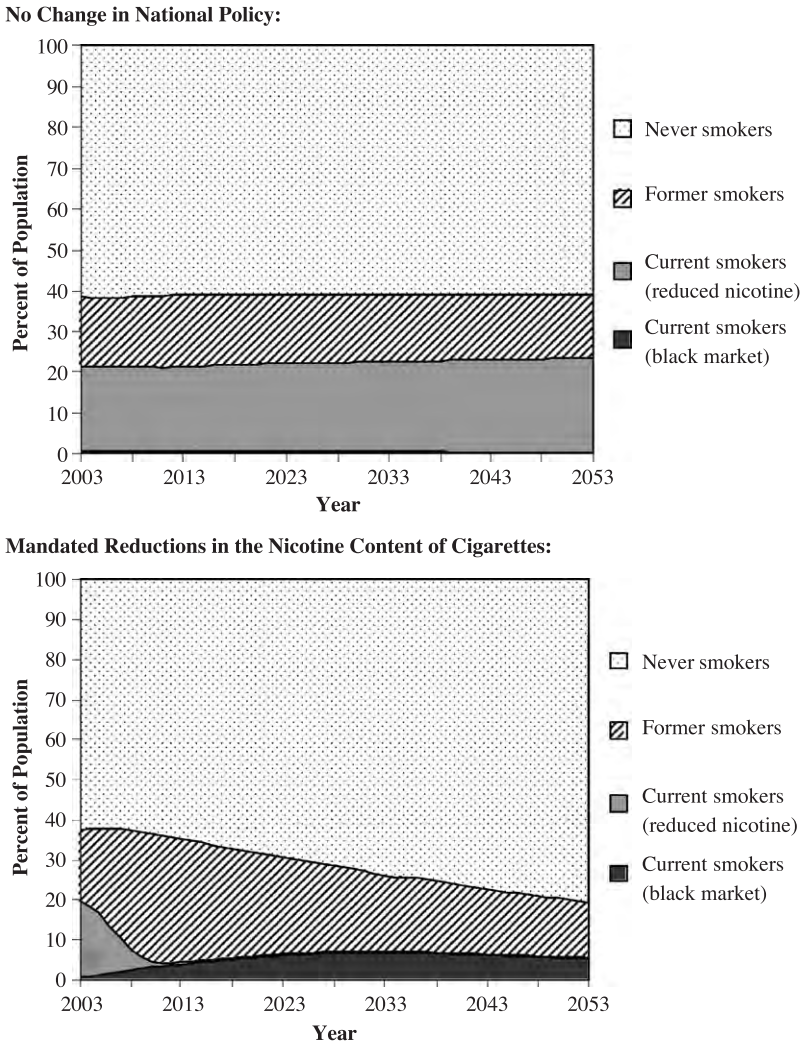

Fig. 2. Estimated prevalence of current, former, and never smokers over 50 years.

captured here with QALYs. Assuming the baseline parameters described previously (an 80% change in smoking behavior, a 10% increase in the mortality of current smokers due to compensation, and 10% of smokers assumed to enter the black market annually), our simulation model estimates that the cumulative gain in QALYs will be approximately 157 million over 50 years.

Because of uncertainty about the extent to which people will change their smoking behavior when faced with reductions in nicotine, as well as uncertainty about the mortality implications of any compensatory smoking that may occur, we performed a two-way sensitivity analysis. We varied the behavior change (initiation, cessation, and relapse) and mortality parameters from 0% to 100%, holding constant all other model parameters at baseline values. Results appear in Table 1. A threshold is evident between the shaded areas, where parameter combinations are such that QALYs are expected to be lost, and unshaded areas, where QALYs are expected to be gained. From examining this threshold, it is clear that if behavior changes by 20% or more, then even if compensatory smoking is serious enough that mortality in smokers increases substantially, the net change in QALYs to the US population is anticipated to be positive rather than negative.

Table 1
Cumulative change in quality-adjusted life-years (in millions) over 50 years depending on the change in tobacco use behavior and the increase in mortality due to compensatory smoking

Increase in Mortality \ Behavior Change	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	0	46	73	92	108	122	134	147	158	170	182
10%	-9	40	68	89	105	120	133	145	157	169	181
20%	-17	34	64	85	103	117	131	144	156	168	180
30%	-26	28	60	82	100	115	129	142	155	167	179
40%	-34	22	55	79	97	113	127	141	153	166	179
50%	-43	17	51	75	95	111	126	139	152	165	178
60%	-51	11	47	72	92	109	124	138	151	164	177
70%	-59	6	43	69	89	107	122	136	150	163	176
80%	-67	0	39	66	87	105	120	135	149	162	176
90%	-75	-5	35	63	84	102	119	133	148	161	175
100%	-83	-11	31	59	82	100	117	132	146	160	174

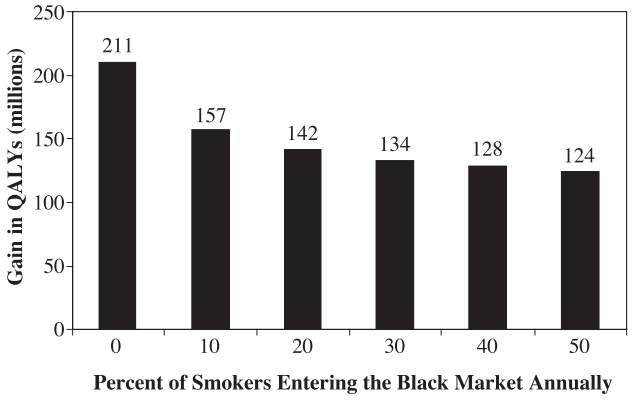

Fig. 3. Cumulative gain in quality-adjusted life-years (in millions) over 50 years. Depending on the percent of additional smokers beginning to purchase cigarettes in the black market annually.

Another key uncertainty in the model is the extent to which smokers will turn to the black market to purchase regular nicotine cigarettes. We initially assumed that, in addition to the approximately 4% of smokers who are currently in the black market, an additional 10% would decide to buy illegal cigarettes annually by the end of 6 years. We varied this latter assumption in a one-way sensitivity analysis, holding all other parameters constant at baseline values. Results, shown in Fig. 3, indicate that the expected gain in QALYs differs depending on the emergence of a black market. At one extreme, if no additional smokers join the black market, then 211 million QALYs may be gained. At the other extreme, if as many as 50% of those who continue to smoke following a mandate start to purchase their cigarettes in the black market annually, then a gain of 124 million QALYs is estimated. Although the magnitude of QALYs differs, it is noteworthy that, at least over this range of plausible estimates, QALYs are uniformly gained rather than lost regardless of the extent of black market entry.

A delay in federal action may mean that in the interim, generations of new smokers will become addicted to nicotine. Fig. 4 shows the number of people who are likely to begin smoking as a function of the number of years delay in congressional action. For example, compared with immediate action, a delay of 10 years would mean that an additional 16 million people may begin smoking during that decade. A delay of 30 years may mean an additional 52 million smokers would become addicted in the interim.

Conclusions

The American Medical Association has boldly advocated that tobacco manufacturers be required to reduce nicotine levels in cigarettes. Supporters of the AMA's position [6,7] point to the generations of young people who will be deterred from smoking, the disease that will be prevented, and the costs associated with treating those diseases that will be avoided. Critics [62], however, have voiced concerns that lowering nicotine levels would only induce smokers to "compensate" by smoking more cigarettes or smoking in ways that are even more harmful to their health to maintain their nicotine consumption. In addition, detractors are worried that a black market will emerge offering ready availability of cigarettes that may be more harmful. By incorporating all of these concerns, both positive and negative, we were able to assess the net implications of a federal mandate for the nation's health. Our intent is to inform the debate surrounding this important policy decision.

Our results reveal that the cumulative impact on the health of US citizens is likely to be overwhelmingly positive rather than negative. The 157 million gain in QALYs estimated by our model, when divided by the size of the current US population, represents an increase of over half of

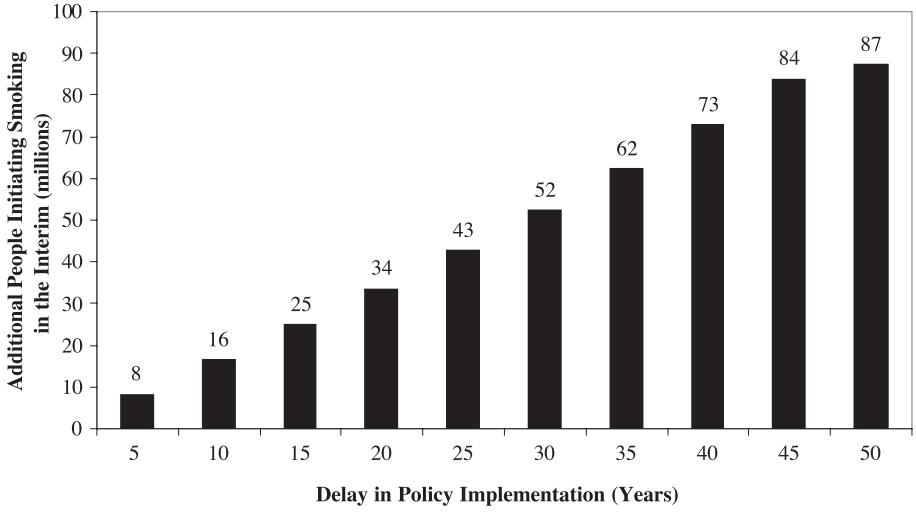

Fig. 4. Estimated number of new smokers with any delay in federal mandate.

a QALY for every man, woman, and child, or, equivalently, a gain of over five QALYs for 10% of the population. Policy makers would be hard-pressed to identify another domestic public health intervention, short of historical sanitation efforts, that has offered this magnitude of benefit to the population.

Some of the parameters included in our model, like all models, are based on imperfect data. Because of this, we assessed whether our results are likely to remain robust over a range of parameter values. In particular, because the extent to which smokers will quit is uncertain, as are the mortality implications of any compensatory smoking they might engage in, we varied these estimates in a two-way sensitivity analysis. We found that the direction of the gain or loss in QALYs, and the magnitude of that change, is dependent on both parameters. Nevertheless, our threshold analysis reveals that as long as smoking cessation increases by 10% or more, smoking relapse and initiation decrease by 10% or more, and compensation is such that mortality in smokers increases by 80% or less, a net gain in QALYs is likely. Because it seems plausible that smokers will quit at high rates after nicotine is reduced to non-addictive levels, and because any mortality risks due to compensatory smoking are likely to be modest compared with the excess risk already faced by smokers, we are confident that our results and final conclusions are robust in the face of these uncertainties. Lowering the nicotine level in cigarettes is likely to substantially improve the health of US citizens.

Policy makers and opinion leaders wishing to rely on our results will want to bear in mind the limitations of this research. Our simulation has two general classes of limitations, those that result from irreducible uncertainty about what may occur following a federal mandate, and those that result from choices we made during the modeling process. The first class of limitations includes the possible growth of a black market, something that is unknown and unknowable. To assess the importance of this parameter, we varied the percent of smokers entering the black market annually up to 50%, a plausible upper bound. We found that over this entire range of increase in black market activity, there is still likely to be a net gain in QALYs. This can be explained by a predictable chain of events: To begin, note that if some percent of current smokers not in the black market enter it every year, eventually virtually all of those smokers will end up in the black market. However, as nicotine is lowered to trace levels, there will be a severe drop in the size of the pool of current smokers who might be potential consumers of smuggled cigarettes. Thus, even if a huge fraction of persistent smokers (e.g., 50%) decide to purchase cigarettes in the black market, a large percent of a small group is a relatively modest number of people.

Other limitations follow from informed choices we made during the modeling process. Our simulation model, like all such models, is "bounded." This means that it attempts to simulate some phenomena but not others. For example, The Tobacco Policy Model simulates the use of the most prevalent form of tobacco, cigarettes, but does not explicitly simulate the use of other types of tobacco such as pipes, cigars, chew, or snuff. We omitted these types of tobacco because the prevalence of use is currently low. For example, less than 2% of men and less than 0.1% of women smoke pipes [63]. Smokeless tobacco is also used almost exclusively by men, mostly athletes or military personnel living primarily in the southeast [64]. Cigar use soared in the 1990s but this fashion trend has since waned [65,66]. Nevertheless, however unpopular these other forms of tobacco are today, it is possible that some cigarette smokers, when faced with reduced nicotine, will switch to these other products to satisfy their craving for nicotine. There is evidence for this "substitution effect," particularly in the literature on excise taxation. For example, Ohsfeldt et al. [67] found that taxing cigarettes may increase the use of smokeless tobacco. In any case, although not modeled here, Congress or the FDA might be well advised to mandate nicotine reductions, not just in cigarettes, but in all tobacco products sold in the United States, thus minimizing switching behavior.

Our model is also bounded in the sense that we consider only population health gains and not other societal impacts. Although we consider the emergence of a black market, we do so strictly for the purpose of assessing its direct effect on population health through the continuing availability of regular nicotine cigarettes. Yet, black markets have other important impacts as well, particularly on crime and the economy. Drug and alcohol prohibition policies and their resultant black markets have contributed substantially to homicide rates [68]. The demand for products that cannot be obtained through legal means finances an underground economy from which such violence arises [69]. Also not included are enforcement costs, medical cost savings from the reduction of tobacco-related disease, or cost increases from medical utilization during a now longer life span. While important, these other ramifications are beyond the scope of the present research, which seeks to understand the population health impacts that are directly related to changes in tobacco use.

While some of the bounds limiting our model may lead us to overestimate the impact of a federal mandate, other bounds result in the underestimation of health gains. Most importantly, we simulate gains over a relatively short period, 50 years. However, any reductions in tobacco use that occur over this period are likely to persist well into the future, perhaps indefinitely. There may be dynamic inter-generational effects such as in the case where a female youth who quits smoking during this time period is then less likely to smoke later during pregnancy. Of course, her infant will be healthier; but in addition, once that infant becomes a teenager, it may

also be less likely to smoke as there is some evidence that babies exposed to nicotine in utero are more likely to smoke later in life, even controlling for post-birth exposure and other factors [70]. Parents who do not smoke will avoid exposing their children to the health hazards associated with environmental tobacco smoke [71]. Teenagers who see fewer movie stars smoking on television may be less enamored with cigarettes. In short, the development of a tobacco-intolerant society will likely be self-reinforcing. Taken together, these dynamic and synergistic effects may result in declines in tobacco use even greater than those estimated here.

Although the present analysis considers a particular approach, mandating nicotine reduction in cigarettes, we do not mean to suggest that this is the only viable approach to reducing tobacco use. A more direct method of "harm reduction" might be to mandate that tobacco manufacturers produce cigarettes that are not necessarily lower in nicotine, but lower in "tar" which causes most smoking-induced diseases. In other research, we evaluated the population health impacts of this alternate approach to harm reduction [72]. Beyond harm reduction, other approaches that are likely to be effective in reducing tobacco use include raising the legal smoking age to 21, anti-tobacco advertising, and increasing tobacco excise taxes.

Furthermore, any nicotine reduction mandate will likely be attempted only with additional supportive measures. As nicotine levels are reduced, there will likely be a sharp increase in the number of smokers who want to quit. Many will visit their physicians seeking nicotine replacement therapy to aid cessation or relief from withdrawal symptoms such as depression [73]. Treatment offered by health care professionals, particularly during the initial 6-year period of this mandate, will be invaluable in ensuring the mandate's success.

Our results reveal that, if implemented, the AMA's ambitious proposal to require tobacco manufacturers to gradually reduce the nicotine content of cigarettes sold in the US is likely to achieve large and persistent gains to the nation's health. We acknowledge in this research that this proposed policy is not a panacea; a black market is likely to emerge and compensatory smoking is likely to increase the excess risk already faced by smokers. However, even considering these negative side effects, important population health gains are likely to be realized. Removing nicotine, the main reason that people smoke cigarettes, will likely deter the use of this hazardous product. Generations of youth will be discouraged from smoking, disease will be averted, and lives will be saved. Any delay in federal action will mean scores of new smokers will become addicted in the interim. These results should aid Congress as they consider legislation directed at manufacturers or contemplate giving the Food and Drug Administration the authority to regulate tobacco.

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