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Assessing the Likelihood and Magnitude of a Population Health Benefit Following the Market Introduction of a Modified-Risk Tobacco Product: Enhancements to the Dynamic Population Modeler, DPM(+1)

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Researchers and those responsible for evaluating and implementing policies intended to reduce population harm must assess the potential for both intended and unintended consequences associated with those policies. Such assessments should be based on the combined dimensions of magnitude, and thus likelihood, of shifts in exposure patterns needed to produce a population benefit or harm, and magnitude of the expected population benefit or harm. In response to this assessment need, we provide a conceptual description of the dynamic population modeler, DPM(+1), as well as illustrative analyses that estimate the effects on all-cause mortality, life expectancy, and quality of life-adjusted life expectancy if exposure patterns in the population shift from a higher risk product (e.g., cigarettes) to a lower, or modified, risk tobacco product (MRTP) in specified ways. Estimates from these analyses indicate that, within a single birth cohort, switching completely from cigarette smoking to MRTP use is more likely to lead to a population-level survival benefit than initiating tobacco use with an MRTP instead of cigarettes. This is because tobacco initiation rarely occurs beyond young adulthood, whereas continuing smokers exist in all subsequent age categories, leading to a greater cumulative effect. In addition, complete switching to MRTP use among a small proportion of smokers in each age category offsets the survival deficit caused by unintended shifts in exposure patterns, such as MRTP initiation among never tobacco users followed by transitioning to cigarette smoking and/or cigarette smokers switching to MRTP use instead of quitting.

KEY WORDS: Population simulation; smoking-attributable mortality; tobacco harm reduction policy

1. INTRODUCTION

Conceptually, the success or failure of a public health policy intended to reduce population harm can be determined by measuring changes in population morbidity and mortality. While reductions in these measures are expected and hoped for, unintended consequences that result in harmful exposure patterns can also occur. It is the responsibility of policymakers makers to consider both the intended, beneficial consequences and the potential for unintended, harmful consequences of proposed policies, and to assess the likelihood and magnitude of both.

The decision to pursue a policy can be aided by the use of statistical models that estimate changes in population morbidity and mortality that might result from specified changes in exposure patterns. If properly constructed, statistical models can be used to estimate the proportion of the population that must engage in a beneficial exposure shift to

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counterbalance any harms that might unintentionally result after implementing the policy being considered, or vice versa. Such analyses can provide insights into the magnitude of behavior changes that must occur in order to result in either benefit or harm to a population, and allow researchers and policymakers to rank the likelihood, and thus the importance for prevention, of various unintended consequences.

The dynamic population modeler, DPM(+1),[3] estimates the difference in population-level survival between a counterfactual scenario that allows the use of a higher risk product and/or a lower risk product, and a base case that only allows the use of the higher risk product.[1] Survival estimates can be used to calculate other indicators of population health, including life expectancy (LE), disease-specific mortality, and morbidity surrogates such as quality of life-adjusted life expectancy (QALE).[2,3] Estimating differences in these measures under different exposure scenarios may, in turn, be used to assess the potential effects of a harm reduction policy.

Application of the DPM(+1) to examples relevant to tobacco control stems from the regulatory landscape that emerged with passage of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) in 2009.[4] The Act assigned the responsibility of regulating the tobacco industry to the U.S. Food and Drug Administration (FDA). The Act specified that FDA shall issue a risk modification order if an applicant has demonstrated that a tobacco product will significantly reduce harm and the risk of tobacco-related disease to individual users, and is likely to benefit the health of the population as a whole.[5]

Two intended, beneficial consequences of widespread modified-risk tobacco product (MRTP) availability are switching to MRTP use by some current cigarette smokers who otherwise would have continued to smoke (i.e., "product switching") and initiation of tobacco use with the MRTP instead of cigarettes by some never tobacco users who would have initiated cigarette smoking (i.e., "alternative initiation"). Which beneficial transition is more likely to lead to a population-level survival benefit is a policy-relevant question that the DPM(+1) was designed to address.

[3]DPM(+1) indicates that one product is added in the counterfactual scenario. A second version of the DPM exists, where one product is removed in the counterfactual scenario (DPM(–1)). Versions adding more than one product in the counterfactual scenario may be developed in the future (e.g., DPM(+2)).

Unintended, harmful consequences of widespread MRTP availability may include initiation of MRTP use by some never tobacco users who otherwise would have remained never tobacco users (i.e., "additional initiation"); transitioning to cigarette smoking after initiation of tobacco use with the MRTP by some who would have remained never tobacco users (i.e., "gateway effect"); and, switching to MRTP use by some current cigarette smokers who otherwise would have quit smoking (i.e., "diversion from quitting"). The DPM(+1) can be used to examine the magnitude, and thus likelihood, of beneficial consequences required to offset the potential for population-level survival deficits associated with harmful consequences of increased MRTP availability.

2. METHODS

2.1. Overview of the DPM(+1)

The DPM(+1) allows for age-specific changes, or transitions, in tobacco use at age intervals of identical widths throughout the duration of follow-up; both are specified by the analyst. As a first step, a hypothetical population of individuals who have never used tobacco is defined and initialized to a constant age. Transition probabilities define the exposure patterns to be compared in the base case and counterfactual scenarios, where only one tobacco product is available for use in the base case and one new product (i.e., an MRTP) is added in the counterfactual scenario (Fig. 1).

In the base case, never tobacco users can remain never users or they can begin cigarette smoking; and, cigarette smokers can continue to smoke or they can quit and then relapse to smoking (Fig. 1, top row). Smoking initiation, cessation, and relapse rates are specified by the analyst according to either completely hypothetical rates or actual population rates. The identified rates are entered as either fixed probabilities or as probabilities with some degree of uncertainty (e.g., as random probabilities from a normal distribution, truncated at 0 and 1, with the point estimate of the probability as the mean and an analyst-specified variance). The probability of transitioning to any exposure pattern that is not of interest can be set to zero. Mortality is calculated for each age interval of follow-up by a Poisson model, which defines mortality rates by age, duration of exposure, and duration of exposure cessation among current and

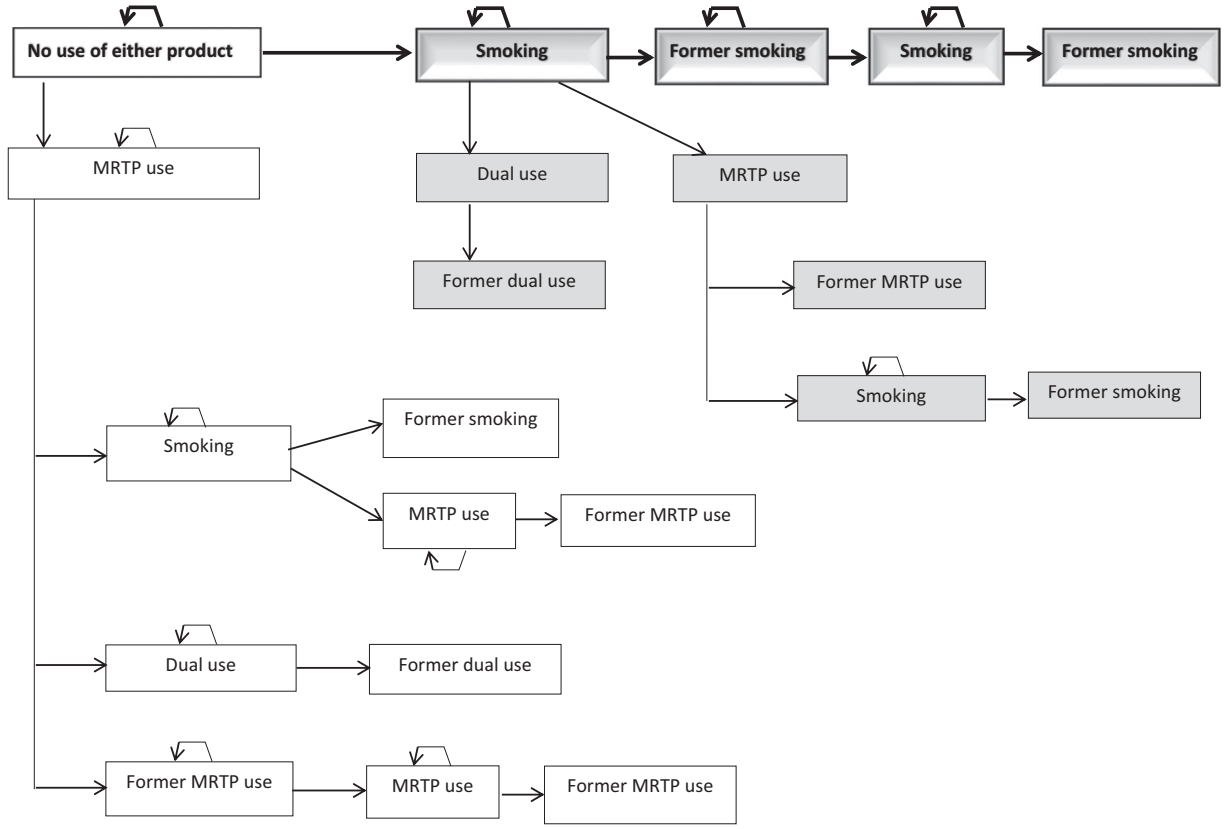


Fig. 1. Schematic representation of the distribution of persons into exposure categories by the DPM(+1); transitions for base case (top row) and counterfactual scenario (all rows); curved arrows represent remaining in the same exposure state.

former cigarette smokers compared to never smokers. Survivors of each age interval move to the next age interval, where they can remain in their current exposure category or transition to a different category. The DPM(+1) provides the number of survivors remaining in the population at the end of each age interval.

The counterfactual scenario assumes that an additional tobacco product (i.e., an MRTP) is available for the population to use (Fig. 1, all rows). Mortality rates for current and former cigarette smokers are calculated using a Poisson model as described above, and are reduced based on excess relative risks (ERRs) to estimate mortality risks for current and former MRTP users. The ERRs compare excess mortality among current and former MRTP users to current and former cigarette smokers, respectively, and are entered as fixed values (when comparing cigarettes to an MRTP with a particular, hypothesized risk profile) or as values with some degree of uncertainty (when a population estimate from the literature is used). The latter are generated using a left-truncated normal distribution, with the point estimate of the ERR as the mean and the variance specified by the analyst. As in the base case, survivors at the end of each age interval move to the next age interval, during which time they can remain in their current exposure category or transition to a different category. Tobacco initiation, switching, cessation, and relapse rates are specified by the analyst, may be hypothetical or based on actual population rates, and may be either fixed values or values that reflect some degree of uncertainty. At the end of each age category, the model provides the number of survivors remaining in the population and compares the numbers of survivors in the counterfactual scenario versus the base case.

The coefficients of the Poisson model that are used to define mortality rates are estimated using a multidimensional Bayesian approach; uncertainty is incorporated using Markov chain Monte Carlo techniques. The prior distribution of each model coefficient is noninformative normal, with mean 0 and standard deviation 100. To guarantee that the

Markov chains converge, 10,000 sets of model coefficients are generated after a burn-in of 2,000 iterations. For the base case and counterfactual scenario, survivors are estimated as described above for each set of Poisson model coefficients (i.e., for each iteration), and means with 95% posterior intervals (95% PI) are reported. The DPM(+1) is executed in the R language.[6]

Although of great importance and interest, morbidity is less easily measured than mortality. Because there is no standard definition of morbidity, there are no methods for effectively measuring or tracking changes in this output measure. QALE approximates population morbidity and is estimated by multiplying LE, calculated according to actuarial principles, by a factor that accounts for disability, illness, or both.[2,3,7–9] We used age-category-specific EuroQol EQ-5D scores from the Medical Expenditure Panel Survey (MEPS) as the adjustment factor and estimated QALE for those surviving to the end of the first age category.[10] The EQ-5D score is an index score reflecting a person's health status based on a brief, standardized questionnaire.[11] Age-category-specific EQ-5D scores from MEPS were adjusted to match the age categories used in the DPM(+1), as shown in Table I.

Table I. Estimated EQ-5D Values Based on Data from the Medical Expenditure Panel Survey (MEPS)

Age Interval	EQ-5D
13–17	0.8505
18–22	0.8505
23–27	0.8333
28–32	0.8219
33–37	0.8150
38–42	0.8104
43–47	0.7957
48–52	0.7859
53–57	0.7811
58–62	0.7779
63–67	0.7579
68–72	0.7445
73–77	0.7013
78-82	0.6725
83–87	0.6725
88–92	0.6725

Notes: MEPS provides EQ-5D values for seven-year age categories, starting at age 18 years, with an open-ended final age category. The EQ-5D value from MEPS age category 18–24 years was used for DPM(+1) age intervals 13–17 and 18–22 years, and the value from MEPS age category 75+ years was used for DPM(+1) age categories 78–82 years and above. For all other DPM(+1) age intervals, the EQ-5D value was calculated as the weighted average of the MEPS EQ-5D values for the adjacent age categories.[10]

2.2. Application of the DPM(+1)

The current illustrative analyses demonstrate the ability of the DPM(+1) to address policy questions relevant to public health and tobacco harm reduction. Specifically, we explored which beneficial transition within a single birth cohort, i.e., product switching or alternative initiation (as defined above), is more likely to lead to a meaningful survival benefit for that cohort. Additionally, we used the DPM(+1) to estimate tipping points, defined as the percentage increase in one or more beneficial transitions required to offset one or more unintended, harmful tobacco use behavior(s), including additional initiation, gateway effect, and diversion from quitting. Tipping points were determined based on a point estimate of 0 (no difference) for the number of survivors in the counterfactual scenario compared to the base case.

For the illustrative analyses, a hypothetical population of 1 million 12-year-old never tobacco users was followed from age 13 years, in five-year intervals, through age 102 years, when the number of survivors is approximately 0 in both the base case and counterfactual scenario. Age-specific mortality rates for never, current, and former smokers were calculated from the Kaiser-Permanente Cohort Study data[12] and the 2000 U.S. Census.[13][4] Results comparing the number of survivors in the counterfactual scenario and base case are presented for the cohort at age 72 years; results after age 72 years are increasingly uninformative, as the number of survivors in both the counterfactual scenario and base case approaches zero.

The base case specifies transition probabilities based on 2009 U.S. cigarette smoking initiation rates[14] and 2005–2008 smoking cessation rates[15] (Table II). More current estimates have been published, but they include as former smokers individuals who quit smoking less than one year in the past. This definition is incompatible with the mortality data for successful smoking quitters (i.e., those who were former smokers for at least two years) from the Kaiser-Permanente Cohort Study. Therefore, the DPM(+1) was calibrated using the 2005–2008 U.S. cessation rates, which define cessation as lasting at least one year. Uncertainty in initiation and cessation rates was accounted for by modeling the transition

[4]Calculations available from the authors.

Table II. Estimated U.S. Smoking Initiation (2009) and Cessation (2005–2008) Rates

Age Interval	Five-Year Smoking Initiation (%)[a]	Five-Year Smoking Cessation (%)[a]
13–17	13.75	N/A[b]
18–22	10.00	9.00
23–27	1.00	9.50
28–32	0.00	14.00
33–37	0.00	14.00
38–42	0.00	14.00
43–47	0.00	14.00
48–52	0.00	14.00
53–57	0.00	14.00
58+	0.00	14.00

[a]Published annual smoking initiation and cessation rates were adjusted to align with the five-year age categories used in the DPM(+1). Values were then multiplied by 2.5 to estimate rates over a five-year period, a conservative estimate of the average person-time at risk of smoking initiation or cessation in each five-year age category.
[b]No smoking cessation allowed in age interval 13–17 years, as smoking duration among quitters in this age interval would only be 2.5 years (on average).

probabilities as truncated normal random variables with means equal to the respective estimates and standard deviations equal to 0.01. An ERR of 0.08, used for these illustrative analyses, was based on a consensus estimate for the mortality risk associated with long-term use of a low-nitrosamine smokeless tobacco product relative to conventional cigarettes. The value of the consensus estimate (adjusted mean; smokeless tobacco use compared to cigarette smoking) was 11.0 for those age 35–49 and 8.2 for those age 50+ years, based on a 100-point scale.[16] Uncertainty in the value of the ERR was accounted for by modeling the ERR as a left-truncated normal random variable with a mean of 0.08 and a standard deviation of 0.01; the standard deviation ensured a range for the ERR of approximately 0.05–0.11.

3. RESULTS

3.1. Product Switching: Smokers Completely Switching to MRTP Use Instead of Continuing to Smoke

To explore this beneficial exposure pattern, the proportion of current smokers who would have continued to smoke cigarettes in the base case but switched completely to and continued to use an MRTP in the counterfactual scenario was increased to 2%, 4%, 6%, 8%, or 10%; MRTP cessation rates were suspended (i.e., no MRTP cessation) in order to define a worst-case scenario. Product switching started in the second age category (ages 18–22 years) and could occur throughout the rest of the follow-up period, thereby affecting all current smokers.

In the counterfactual scenario, where 2% of current smokers who would have continued to smoke instead switched completely to and then continued to use an MRTP, there was a statistically significant survival benefit of 3,127 additional survivors (95% PI: 2,751–3,508) compared to the base case at the end of age category 68–72, a 0.10-year increase in LE at age 18 years, and a 0.07-year increase in QALE at age 18 years (Table III). The difference in the number of survivors comparing the counterfactual scenario to the base case increased with increasing proportions of smokers switching completely to an MRTP instead of continuing to smoke.

3.2. Alternative Initiation: MRTP Initiation among Those Who Would Have Initiated Smoking

For the second beneficial exposure pattern, 5%, 10%, 20%, or 50% of those who would have initiated cigarette smoking in the base case instead initiated and then continued to use an MRTP in the counterfactual scenario; MRTP cessation rates were again suspended. Based on U.S. population rates (Table II), cigarette initiation among never tobacco users occurs in the first three age categories, i.e., from age 13 to 27 years. Thus, for this analysis, MRTP initiation among never tobacco users who would have remained never tobacco users in the base case was also allowed to occur from ages 13 to 27 years.

In the counterfactual scenario with 5% alternative initiation, there was a statistically significant survival benefit of 909 additional survivors (95% PI: 777–1,047) and a 0.03-year increase in LE at age 18 years (0.02 years after adjusting for quality of life), compared to the base case (Table III). The benefit at the population level grew with increasing proportions of alternative initiation among never tobacco users, i.e., MRTP use by those who would otherwise have initiated cigarette smoking. If, for example, 10% of those who would have initiated cigarette smoking instead initiated and then continued to use an MRTP, there would be an estimated 1,818 additional survivors (95% PI: 1,554–2,093) at the end of age category 68–72 years (counterfactual scenario compared to the base case), a 0.05-year increase in

Table III. Smokers Switching Completely to MRTP Use Instead of Continuing to Smoke (Product Switching)[a]

Current Smokers Who Switch to MRTP Use (%)	Difference in Survivors at Age 68–72 Years	95% PI		Difference in LE at Age 18 Years[b]	Difference in QALE at Age 18 Years[b]
2	3,127	2,751	3,508	0.10	0.07
4	5,989	5,270	6,720	0.20	0.14
6	8,610	7,574	9,660	0.28	0.20
8	11,011	9,685	12,354	0.36	0.26
10	13,213	11,619	14,827	0.43	0.31

[a]Switching from cigarettes to MRTP can occur in all age categories (except for the first age category) and can affect all current smokers.
[b]Life expectancy (LE) at age 18 years and quality of life-adjusted life expectancy (QALE) at age 18 years based on follow-up through age 102 years.
Notes: Differences between counterfactual scenario and base case for "number of survivors in age interval 68–72 years," "LE at age 18 years," and "QALE at age 18 years."

Table IV. MRTP Initiation among Those Who Would Have Initiated Smoking (Alternative Initiation)[a]

Never Users Who Initiate MRTP Use Instead of Cigarettes (%)	Difference in Survivors at Age 68–72 Years	95% PI		Difference in LE at Age 18 Years[b]	Difference in QALE at Age 18 Years[b]
5	909	777	1,047	0.03	0.02
10	1,818	1,554	2,093	0.05	0.04
20	3,636	3,108	4,186	0.10	0.08
50	9,089	7,770	10,466	0.25	0.19

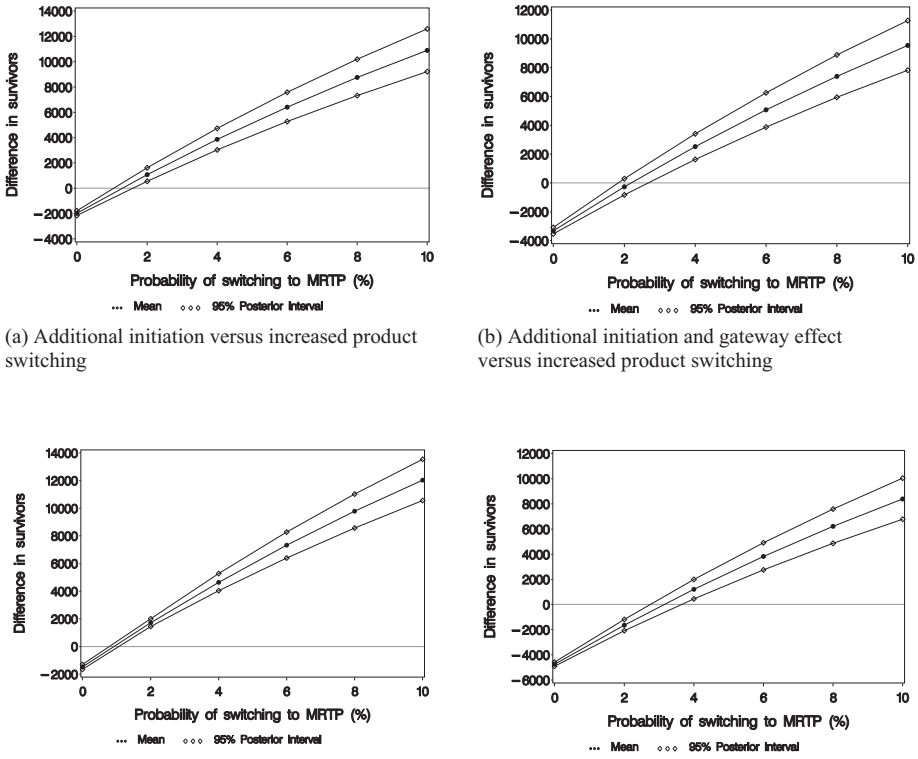
[a]Smoking and MRTP initiation can occur in the first three age categories (ages 13–17, 18–22, and 23–27 years).
[b]Life expectancy (LE) and quality of life-adjusted life expectancy (QALE) at age 18 years based on follow-up through age 102 years.
Notes: Differences between counterfactual scenario and base case for "number of survivors in age interval 68–72 years," "LE at age 18 years," and "QALE at age 18 years."

LE at age 18 years, and a 0.04-year increase in QALE at age 18 years (Table IV). Thus, within a single birth cohort, alternative initiation among those who would have initiated cigarette smoking was less likely to lead to a population benefit than complete product switching among those who would have continued to smoke cigarettes. For example, a survival benefit of ~9,000 additional survivors resulted from 50% of base case smoking initiators instead initiating and continuing to use an MRTP (Table IV). To achieve a similar survival benefit, ~6% of base case continuing cigarette smokers would have to switch completely to and continue to use an MRTP in the counterfactual scenario (Table III).

3.3. Tipping Point: Additional Initiation Versus Increased Product Switching

Based on U.S. population rates (Table II), cigarette initiation among never tobacco users occurs in the first three age categories, i.e., from age 13 to 27 years. Thus, for this tipping point analysis of harmful and beneficial exposure patterns, MRTP initiation among never tobacco users who would have remained never tobacco users in the base case was also allowed to occur from ages 13 to 27 years. To represent an extreme scenario, MRTP initiation rates in the counterfactual scenario were set to 50% of the U.S. smoking initiation rates applied in the base case (Table II), and MRTP cessation was suspended. In addition, complete switching from cigarettes to MRTP use among smokers who would have continued to smoke in the base case was increased to 2%, 4%, 6%, 8%, or 10% in the counterfactual scenario; switching could occur beginning in the second age category (ages 18–22 years) and continued through the end of the follow-up period, affecting all current smokers.

Note that in the absence of any gateway effect, MRTP initiation among base case never tobacco users in a particular age category reduces the pool of those available to initiate tobacco use with cigarettes



(a) Additional initiation versus increased product switching

(b) Additional initiation and gateway effect versus increased product switching

(c) Diversion from quitting versus increased product switching

(d) Additional initiation and gateway effect combined with diversion from quitting versus increased product switching

Fig. 2. Graphical representation of tipping point analyses; differences between counterfactual scenario and base case in number of survivors through follow-up.

in the next age category. Therefore, in the scenarios described here, the harmful effect of MRTP initiation among base case never tobacco users was slightly offset by the beneficial effect of a concurrent decrease in the number of smokers in the population. Specifically, starting in the third age category and throughout follow-up, the number of current and former smokers was ~ 3% higher in the base case compared to the counterfactual scenario (data not shown).

With MRTP initiation among base case never tobacco users set to 50% of U.S. smoking initiation rates, there would be an estimated 1,969 fewer survivors (95% PI: –2,155 to –1,772) in the counterfactual scenario compared to the base case at the end of age category 68–72 years, a 0.07-year decrease in LE at age 18 years, and a 0.05-year reduction in QALE at age 18. For a concurrent ~1.3% increase in the proportion of current smokers who switched completely to MRTP use instead of continuing to smoke, the decrease in survivors due to increased MRTP initiation would be completely offset. As a result, the point estimate for the difference in the number of survivors between the counterfactual scenario and the base case would be 0 (Fig. 2a), as would the difference in LE and QALE at age 18 years. If there was a concurrent ~1.6% increase in the proportion of current smokers who switched completely to MRTP use instead of continuing to smoke, there would be a statistically significant survival benefit in the counterfactual scenario compared to the base case (Fig. 2a).

3.4. Tipping Point: Additional Initiation and Gateway Effect Versus Increased Product Switching

Similar to the previous tipping point analysis, cigarette initiation and MRTP initiation occurred in the first three age categories, i.e., from ages 13 to 27 years. MRTP initiation rates in the counterfactual scenario were set to 50% of the U.S.

smoking initiation rates applied in the base case (Table II), and MRTP cessation was suspended. To examine a gateway effect, 20% of MRTP initiators switched to cigarette smoking in the age category following MRTP initiation, i.e., in age categories 18–22, 23–27, and 28–32 years. As a point of reference, about 20% of smoking experimenters reportedly transition to regular smoking.[17] Product switching from cigarette to MRTP use among smokers who would have continued to smoke in the base case was increased to 2%, 4%, 6%, 8%, or 10% in the counterfactual scenario, starting in the second age category (ages 18–22 years) and continuing until the end of follow-up.

Absent the benefits of product switching, there were an estimated 3,318 fewer survivors (95% PI: –3,530 to –3,100) in the counterfactual scenario compared with the base case at the end of age category 68–72, a 0.10-year reduction in LE at age 18 years, and a 0.07-year reduction in QALE at age 18 years. A concurrent ~2.2% increase in product switching (i.e., the proportion of current smokers who switched completely to MRTP use instead of continuing to smoke) would completely offset the decrease in survivors due to additional initiation combined with a gateway effect. As a result, the point estimate for the difference in the number of survivors between the counterfactual scenario and the base case would be 0 (Fig. 2b), as would the difference in LE and QALE at age 18. If there was a concurrent ~2.7% increase in the proportion of current smokers who switched completely to MRTP use instead of continuing to smoke, there would be a statistically significant survival benefit in the counterfactual scenario compared to the base case (Fig. 2b).

3.5. Tipping Point: Diversion from Quitting Versus Increased Product Switching

For this tipping point analysis, smoking cessation was set to 50% of levels specified in the base case to represent an extreme scenario (i.e., half of those who would have quit smoking in the base case instead transition to MRTP use; Table II), and MRTP cessation rates were suspended. Complete switching from cigarette to MRTP use among smokers who would have continued to smoke in the base case was increased to 2%, 4%, 6%, 8%, or 10% in the counterfactual scenario, starting in the second age category (ages 18–22 years) and continuing throughout the follow-up period.

Based on estimated differences in survivors for the counterfactual scenario compared to the base case, if 50% of those current smokers who would have quit smoking (and hence all tobacco use) in the base case instead switch to MRTP use, there would be an estimated 1,477 fewer survivors (95% PI: –1,655 to –1,303) at the end of age category 68–72, a 0.05-year reduction in LE at age 18 years, and a 0.04-year reduction in QALE at age 18 years. A concurrent ~0.9% increase in product switching (i.e., the proportion of current smokers who switched completely to MRTP use instead of continuing to smoke) would completely offset the decrease in survivors due to diversion from quitting. As a result, the point estimate for the difference in the number of survivors would be 0 (Fig. 2c), as would the difference in LE and QALE at age 18. If there was a concurrent ~1.1% increase in the proportion of current smokers who switched completely to MRTP use instead of continuing to smoke, there would be a statistically significant survival benefit in the counterfactual scenario compared to the base case (Fig. 2c).

3.6. Tipping Point: Additional Initiation, Gateway Effect, and Diversion from Quitting Versus Increased Product Switching

To assess the "net" impact on population health for the combined harmful tobacco exposure patterns, MRTP initiation rates in the counterfactual scenario were set to 50% of the U.S. smoking initiation rates applied in the base case (as previously described); 20% of MRTP initiators were allowed to transition to cigarette smoking in the next age interval (as previously described); and 50% of those smokers who would have quit cigarettes (and thus all tobacco use) in the base case instead switched to and then continued to use an MRTP in the counterfactual scenario (as previously described). For the beneficial exposure pattern, complete switching from cigarette smoking to MRTP use among smokers who would have continued to smoke in the base case was increased to 2%, 4%, 6%, 8%, or 10% in the counterfactual scenario, starting in the second age category (ages 18–22 years) and continuing throughout the follow-up period.

Based on estimated differences in survivors for the counterfactual scenario compared to the base case, increasing the proportion of MRTP initiators and then transitioning 20% of MRTP initiators to cigarette smoking in the next age category, combined with decreasing the proportion of cigarette quitters by 50%, would result in an estimated 4,756 fewer sur-

vivors (PI: –4,913 to –4,590) at the end of age category 68–72, a 0.15-year reduction in LE at age 18 years, and a 0.11-year reduction in QALE at age 18 years. A concurrent ~3.2% increase in product switching (i.e., the proportion of current smokers who completely switched to MRTP use instead of continuing to smoke) would completely offset the decrease in survivors due to additional initiation combined with a gateway effect and diversion from quitting. As a result, the point estimate for the difference in the number of survivors would be 0 (Fig. 2d), as would the difference in LE and QALE at age 18 years. If there was a concurrent ~3.7% increase in the proportion of current smokers who switched completely to MRTP use instead of continuing to smoke, there would be a statistically significant survival benefit in the counterfactual scenario compared to the base case (Fig. 2d).

4. DISCUSSION

The current illustrative analyses assessed which of the intended, beneficial exposure patterns, i.e., product switching or alternative initiation, would be more likely to lead to a population benefit. Additionally, we conducted tipping point analyses to examine the magnitude, and thus likelihood, of product switching required to offset the population harm that may be associated with unintended consequences of widespread MRTP availability, individually and in combination.

Applying our selected input values to a single birth cohort, we found that product switching, i.e., complete switching from cigarette smoking to the use of a lower risk product, was more likely than alternative initiation to lead to a population benefit. We also found that a small proportion of smokers in each age category completely switching to an MRTP that presents substantially lower mortality risk than cigarette smoking would offset the population harm caused by unintended changes in tobacco use behaviors that may be associated with widespread availability of an MRTP, e.g., additional initiation followed by gateway effect or diversion from quitting. There are two reasons for this finding. First, switching to a lower risk product can occur throughout follow-up, because continuing smokers exist in all age categories. In contrast, population data indicate that initiation of tobacco use—in particular, with cigarettes—predominantly occurs prior to age 23 years. Additionally, because we operationalized the harmful exposure pattern, gateway effect, as a proportion of those who initiated tobacco use with an MRTP transitioning to cigarette smoking in the next age category, this transition only operates during age categories 18–22, 23–27, and 28–32 years. Second, as previously noted, smoking initiation rates are applied to all nonsmokers in an age category, but the population available to initiate tobacco use with cigarettes is slightly smaller in the counterfactual scenario than in the base case. This is because some base case nonsmokers initiate tobacco use with an MRTP in the counterfactual scenario, leaving them eligible to switch to cigarettes but not to initiate tobacco use with cigarettes. Thus, the harmful effect of MRTP initiation among base case never tobacco users is slightly offset.

The current analyses demonstrate the capabilities of a flexible tool, the DPM(+1), to estimate the effects on all-cause mortality, LE, and QALE that might be associated with different patterns of exposure as a population shifts from higher to lower risk products in specified ways. We developed the DPM(+1) to assess the effects of different tobacco exposure scenarios, with the goal of informing regulatory decision making as outlined in the FSPTCA regarding MRTPs.[4] Models are useful in this context to predict the magnitude, and thus likelihood, of changes in exposure patterns needed to produce a population benefit and/or likely to produce a population harm. While reducing a harmful exposure in individuals (i.e., due to product switching) logically should lead to reduced population harm, increases in population harm might nonetheless occur if more people begin using tobacco and/or if fewer people stop using tobacco because of the availability of an MRTP. The DPM(+1) can be used to explore what would happen to a hypothetical population at different attained ages, under different counterfactual scenarios. A range of probabilities can be modeled for each transition of interest to determine the potential magnitude and likelihood of a population benefit or harm.

The choice of output measures (differences in numbers of survivors, LE, or QALE) depends on the question being addressed by a given analysis. Specifically, the difference in the number of survivors under two exposure scenarios provides a direct estimate of the effect on population health. LE estimates can be used to plan for the delivery of healthcare, while QALE estimates provide a measure that approximates morbidity and is used by economists to choose between medical interventions competing for the same resources.[2,3,9,18] Because the vari-

ous output measures produced by the DPM(+1) are calculated from the same default output, i.e., the difference in the number of survivors, each provides a different view on the same information. Nevertheless, interpretation of the different measures requires additional attention, as a seemingly large magnitude of difference in one measure (difference in survivors) may seem small when expressed another way (LE or QALE). The current analyses highlight this issue, and they are comparable to other analyses of mortality and LE differences. For example, using U.S. data from 1995, Wagener *et al.* estimated that a (seemingly large) 5% reduction in age-specific mortality produced only about 0.5 additional years of LE.[19]

Modeling results are highly dependent on the input data selected by the analyst. For these illustrative analyses, transition probabilities for the base case were selected based on 2009 U.S. cigarette smoking initiation rates and 2005–2008 cessation rates, with age- and tobacco-exposure-specific all-cause mortality risks proportional to those of males who participated in the Kaiser-Permanente Cohort Study.[12] Mortality risks from other populations and cigarette smoking initiation and cessation rates from other time periods, if available, may be more informative for other analyses. For example, for alternative initiation and product switching, differences in survivors between the counterfactual scenario and the base case would be attenuated if lower smoking initiation and higher cessation rates were used because of the reduction in the number of smokers and the resulting decrease in the number of MRTP users.

Transition probabilities defining the counterfactual scenarios were selected to describe extreme scenarios for harmful consequences that could be associated with the widespread availability of an MRTP in the U.S. market; however, these transition probabilities can be modified in the DPM(+1) to model different scenarios of interest. And while the illustrative analyses presented are relatively simple, the DPM(+1) can be used to model more complex scenarios that incorporate additional shifts in exposure patterns including, but not limited to, MRTP cessation and relapse and concurrent use of both MRTP and cigarettes. Increasing the number and type of exposure patterns in the counterfactual scenarios would likely provide a closer approximation to actual consumer behaviors, and could suggest other patterns of increased or decreased population harm, but might be limited by the difficulty of identifying reliable model input values. Defining the exposure patterns of key concern is a necessary challenge for those engaged in developing policies, and these should be the focus of any analyses undertaken. Defining the level of change from the baseline number of survivors that is both likely to occur and large enough to impact population health is a separate decision, and one that should be undertaken collaboratively with all the relevant stakeholders, preferably *a priori*.

Aside from the specific exposure patterns selected to define the base case and counterfactual scenarios, additional input parameters that influence the results produced by the DPM(+1) include the magnitude of the ERR selected to describe an MRTP under consideration, the amount of uncertainty specified for the input parameters, and the duration of follow-up; all of these parameters are defined by the analyst. The output metric selected for a given analysis (differences in numbers of survivors, LE, or QALE) must be interpreted in light of the input parameters, and a judgment must be made regarding the relative population benefit or harm identified. Care must be taken in defining meaningful differences, and the rationale for these decisions should be documented.

In spite of these cautionary notes, the DPM(+1) is expected to provide valuable information to policymakers choosing between different courses of action. The DPM(+1) is the only population model, developed to support tobacco regulations, that has the ability to estimate tipping points. Such analyses are essential in the regulatory context because they allow for the examination of the magnitude, and thus likelihood, of consequences of increased availability of the proposed MRTP. The various output measures can be used to address different questions based on identical input and assumptions, assuring consistency and comparability of analyses and results. Assessing the magnitude of beneficial and harmful shifts in exposure patterns, including associated tipping points, should aid in making rational choices on whether or not to support a particular policy regarding the introduction of an MRTP into the market. Because all input parameters are specified by the analyst, specific exposure patterns of interest can be investigated.

Like all models, the DPM(+1) is built on simplifying assumptions, as follows: (1) it compares the effects of using only two types of tobacco products; (2) it assumes that the rates of risk reduction associated with quitting different types of tobacco use (e.g.,

cigarettes and MRTP) are proportional; for the current analyses, MRTP cessation was suspended; (3) mortality rates are dependent on the overall duration of product use or quitting, but not on either the amount of each product used or on the sequence of exposures; (4) only the direct effects of exposure to higher and lower risk tobacco products are considered; hence, the current analyses do not account for changes to second-hand smoke exposures, for example, which are due to changes in the proportions of cigarette smokers in the population; and (5) the model requires the analyst to specify values of the relevant input data; however, because the outcome measures depend on the precision of the input data, precision is estimated for differences in the number of survivors in the base case and counterfactual scenarios.

Alternative analytic frameworks have been suggested for assessing the population benefit or harm that may result from specified shifts in tobacco exposure patterns. In particular, some researchers have suggested models that employ a framework whereby simulations start with a cross-sectional population of mixed ages, genders, and tobacco use status (never users, former users by years since quitting, and current users).[20–22] Each age in the cross-sectional population represents a distinct birth cohort, which is followed over time (based on calendar year and age), with new members added through births and existing members removed through deaths. While such models purport to predict future mortality under the assumption that an MRTP is introduced during the follow-up period, following a cross-sectional population over time to assess population health in this manner is unnecessarily complex, with great input requirements, and raises methodological questions. In particular, such models are limited by short follow-up periods and lack of generalizability.[23]

The main strengths of the DPM(+1) are its flexibility, its ability to account for uncertainty in the model inputs and outputs—one of few published models in the context of tobacco regulation with this capability—and its comprehensiveness. In addition, the DPM(+1) was successfully validated and calibrated, whereby appropriate input data were used to define a base case and a counterfactual scenario whose model results showed close correspondence to data from an actual population.[1] All model inputs can be changed by the analyst, and the level of uncertainty in model inputs can be specified and is accounted for by the PIs around the estimated differences in the number of survivors. There are no restrictions on age, time of initiation, or time of cessation of exposure.

The key benefit of using models, such as the DPM(+1), is the ability to hold constant all assumptions and factors other than the distribution of exposures or the comparative risk estimates. The model outputs can thus be used to test hypotheses regarding the possible magnitude of benefit or harm that might follow from specified exposure distributions under conditions that are otherwise the same. These analyses do not provide absolute predictions of differences in survival due to changes in tobacco exposure patterns, but they do show the magnitude of behavior changes that must occur in order to result in either benefit or harm to a population. They also allow for researchers and policymakers to rank the likelihood, and thus the importance for prevention, of various unintended consequences.

The examples presented here are not meant to be exhaustive, but they do reflect concerns that have been raised regarding potential unintended consequences that may be associated with the widespread availability of an MRTP in the marketplace. They are meant to provide a conceptual description of the capabilities of the DPM(+1) by showing the types of results that can be produced, and to support those charged with making choices between different policies by providing methods for objectively considering the magnitude and likelihood of both intended, positive consequences and unintended, negative consequences of their choices. Based on these examples, we demonstrated that switching completely from cigarette smoking to MRTP use is more likely to lead to a population-level survival benefit than initiating tobacco use with an MRTP instead of cigarettes. In addition, complete switching to MRTP use among a small proportion of smokers in each age category offsets the survival deficit that might be expected due to extreme scenarios for MRTP initiation among never tobacco users, followed by transitioning to cigarette smoking, and/or cigarette smokers switching to MRTP use instead of quitting.

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