BMJ Open

Markov-model cost-effectiveness evaluation of a cessation programme when tobacco policies are comprehensive

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To cite: Mussio I, Triunfo P, Gerstenblüth M. Markov-model cost-effectiveness evaluation of a cessation programme when tobacco policies are comprehensive. *BMJ Open* 2026;**16**:e113050. doi:10.1136/bmjopen-2025-113050

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-113050).

Received 28 October 2025
Accepted 04 February 2026

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ABSTRACT

Objectives This study conducts a cost-effectiveness analysis of the Tobacco Treatment Programme (TTP) of Uruguay's National Resource Fund (NRF), within the context of the country's advanced implementation of tobacco control policies.

Design We run a 10 000 Markov model simulation with three states (people who smoke, people who have quit smoking and death) to simulate the trajectories of a cohort. The model has been widely used in previous studies evaluating smoking cessation interventions.

Participants For the simulations, we use information from the 2016 to 2017 NRF TTP cohort. Nearly half of the participants lived in the capital, one-fifth had tertiary education, and about one-third had public health coverage. Participants began smoking at an average age of 16 years and smoked about 20 cigarettes per day when entering the TTP.

Interventions The process of tobacco cessation is simulated under different alternatives: no intervention, the current TTP (bupropion, nicotine gum and counselling), an expanded TTP that incorporates nicotine patches as a replacement therapy, and a potential future programme with cytisine and counselling (with and without mortality adjustments).

Setting We focus on Uruguay, which has been recognised as a global leader in tobacco control, including 100% smoke-free environments, a full advertising ban, plain packaging and steady tax increases.

Measurements We compare cost-effectiveness of policy alternatives using years of life lost (YLL) and incremental cost-effectiveness ratios, comparing policy alternatives with no intervention and the current tobacco cessation programme in the country. The analysis considers the direct costs of treatments for smoking-related diseases (healthcare perspective) as well as social costs resulting from loss of productivity (societal perspective).

Results The results indicate that all policy interventions lead to a reduction in the YLL compared with no intervention. Among these options, the inclusion of cytisine emerges as the most cost-effective choice. In a scenario including the transition probabilities from the TTP cohort, this alternative would result in a 10.9% reduction in YLL, with a particularly positive impact among women (−16.5% vs −4.0% in men). In terms of cost-effectiveness, the costs per YLL averted would be on average US\$3991 per YLL from a healthcare perspective, and US\$3773 per YLL from a societal perspective.

Conclusions Tobacco cessation programmes in Uruguay are highly cost-effective, and our results justify their expansion and optimisation. The incorporation of cytisine into the TTP and a focus on groups with more severe tobacco consumption are recommended.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We expand the number of illnesses used in a Markov chain simulation for tobacco control to seven, which has not been used before.
⇒ We focus on comparing five policy interventions, including no cessation programme, the current programme and new alternatives with cytisine as nicotine replacement therapy.
⇒ We use a cohort of 10 000 simulations plus 1000 bootstrap resampling methods to generate incremental cost-effectiveness ratios and 95% CIs.

INTRODUCTION

Tobacco control policies have reached high levels of implementation in several countries, leaving limited room for additional gains through taxation or regulation alone. After comprehensive measures such as advertising bans, smoke-free environments, large pictorial warnings and plain packaging are fully adopted, the marginal impact of new regulatory efforts decreases. In these contexts, the remaining potential to further reduce the burden of smoking increasingly depends on the reach and effectiveness of cessation support. Helping people who smoke quit becomes the most effective lever to reduce tobacco-attributable morbidity and premature mortality once the 'easy gains' from tobacco-control policies have been exhausted.

Tobacco cessation programmes are widely implemented worldwide using context-specific approaches. Common strategies include helplines, online services, support groups, behavioural therapies, nicotine replacement therapy (NRT) and prescription medications. Evidence shows these interventions increase quit rates and are among the most cost-effective strategies to reduce tobacco-related disease costs.[1–3] A substantial body of evidence from high-income countries shows that these interventions increase quit rates and are among the most cost-effective strategies to reduce tobacco-related disease and premature mortality. For example, Lee *et al*[4] reviewed hospital-based cessation programmes and reported favourable incremental cost-effectiveness ratios (ICERs), including US$10 550 per year of life gained and US$5680 per quality-adjusted life year (QALY), well within WHO-recommended thresholds. Similarly, Cadham *et al*[5] found that multiple cessation strategies for US people who smoke eligible for lung cancer screening were cost-effective, with ICERs ranging from US$555 to US$35 531 per QALY, while Hoogendoorn *et al*[6] reported substantial life-year gains and high cost-effectiveness of cessation interventions among patients with chronic obstructive pulmonary disease (COPD) in the UK. Evidence from non-hospital and population-based settings further supports these findings, including cost-effective motivational text messaging interventions in primary care in Spain,[3] national cessation programmes in France[2] and paediatric-care-based interventions in the USA.[7]

Beyond QALYs, reductions in years of life lost (YLL) highlight the population-level benefits of smoking cessation. Jha *et al*[8] showed that quitting smoking before age 40 avoids more than 90% of tobacco-related excess mortality and adds approximately 9 years of life expectancy, while Holford *et al*[9] estimated that tobacco control policies in the USA prevented 8 million deaths and saved 157 million life years between 1964 and 2012. Together, this literature underscores the strong economic and public health rationale for investing in cessation support, particularly in settings where regulatory tobacco control measures have already reached maturity.

Evidence outside hospital settings also supports broader population interventions. In Spain, Cobos-Campos *et al*[3] found motivational text messaging in primary care cost-effective, significantly boosting quit rates. Cadier *et al*[2] estimated cessation programmes in France could save €15–215 million over 5 years, with implementation costs of €125–421 million. An innovative US programme, CEASE (Clinical Effort Against Secondhand smoke Exposure), evaluated by Drouin *et al*,[7] targeted parental smoking in paediatric care using NRT, texts and support lines. It was cost-effective, with an ICER of US$1132 per QALY, emphasising the impact of adapting interventions to non-traditional contexts.

While the cost-effectiveness of smoking cessation programmes has been widely documented, most evidence comes from high-income countries and from settings where tax and regulatory policies are still evolving. Far less is known about the performance of cessation interventions in environments where tobacco control policies are already highly developed. In addition, there is almost no economic evaluation of cytisine as a cessation tool in Latin America, and virtually none assessing cost-effectiveness from both the healthcare and societal perspectives in a publicly financed universal healthcare system. The lack of evidence from mature policy environments represents a relevant gap, since the marginal value of cessation support may be higher where traditional regulatory instruments have reached saturation.

In the case of Uruguay, the country has been recognised as a global leader in tobacco control since ratifying the WHO's Framework Convention on Tobacco Control in 2004, which came into force in 2005. The treaty implemented MPOWER strategies including: M (monitoring tobacco use and prevention policies), P (protecting people from tobacco smoke), O (offering help to quit tobacco use), W (warning about the dangers of tobacco), E (enforcing bans on advertising, promotion and sponsorship) and R (raising taxes on tobacco products). These measures led to major milestones such as 100% smoke-free environments (since 2006), a full advertising ban (2014), plain packaging (2020) and steady tax increases, rising from 44% of the retail price of a 20-cigarette pack in 2005 to 65% in 2023, including the addition of value added tax since 2007 (see[10] for a detailed description and timeline of all measures).

The measures have significantly reduced tobacco use: adult smoking dropped by 33% between 2006 and 2022, and youth smoking (ages 13–17) fell by 72% from 2003 to 2021. However, progress has been slower among women and socioeconomically vulnerable groups.[10] Based on the latest available data, in 2024, 20.44% of Uruguayans aged 15–64 smoked, measured as daily or occasional tobacco use.[11] Despite progress, tobacco use remains a leading cause of preventable death in Uruguay, responsible for 15% of total deaths annually, which is comparable to COVID-19 mortality in 2020–2021.[12]

Given the extensive implementation of most MPOWER measures in Uruguay, there is an opportunity to strengthen the 'O' component by expanding and better targeting cessation support. To inform this, we conducted a cost-effectiveness analysis of the Tobacco Treatment Programme (TTP) of the National Resources Fund (NRF), the institution which finances this programme. The NRF is a non-state public entity regulated by law 16 343, operating since 1981. It operates as a reinsurance agency for providing universal financial coverage for highly complex procedures, expensive devices and expensive medications for all residents covered by the National Integrated Health System. We also examined alternative evidence-based medications to improve policy design.

Through Markov model simulations, we compared different policy scenarios: no intervention; the current NRF TTP (including bupropion, nicotine gum and counselling); an expanded NRF TTP that incorporates nicotine patches as replacement therapy; and a potential future programme that adds cytisine alongside counselling. The estimation of YLL and the ICER indicates that the current NRF TTP is a cost-effective intervention, while the inclusion of cytisine as an alternative treatment could enhance both health and economic benefits.

Overall, tobacco cessation programmes have been shown to be highly cost-effective in reducing disease burden. Reviewed studies show favourable ICERs across diverse settings. QALY and YLL estimates reinforce the value of investing in cessation efforts to improve health and reduce tobacco-related costs.

Our study contributes to the literature by using real-world cessation outcomes from a national programme cohort, rather than relying exclusively on international parameters. By incorporating transition probabilities observed in the Uruguayan TTP, our Markov model approach reflects the behaviour of treatment-seeking people who smoke in a mature tobacco control environment. The evaluation compares multiple pharmacological strategies under two perspectives—healthcare costs and societal productivity losses—and uses YLL as the primary outcome, aligning with global disease burden methodologies. This approach allows us to assess not only clinical effectiveness but also economic efficiency and the value of investing in cessation relative to continuing to finance tobacco-related diseases.

We find that while all alternative cessation programme scenarios are cost-effective when compared with no intervention (no cessation scenario), a treatment including cytisine emerges as the most cost-effective option. Cytisine not only produces the largest reduction in YLL but also becomes cost-saving relative to other treatments, reducing both healthcare expenditures and productivity losses. The results are particularly pronounced among women, who gain more years of life and generate lower costs per YLL averted. These findings support policy design and optimisation in Uruguay, including alternative treatments for cessation programmes at the local level, in both private and public health institutions.

This paper is structured as follows: the background section provides a summary of the tobacco treatment and cessation programme of the Uruguayan NRF as well as a short summary of the international evidence. We then provide detailed explanations on the data and the methodology used to evaluate this programme, as well as the different scenarios used in this study. We then discuss the results of the programme evaluation under the different scenarios and conclude with a discussion, including policy recommendations.

BACKGROUND

In 2003, the NRF began implementing programmes to prevent cardiovascular diseases while optimising resource allocation for treating these conditions. A TTP was created after recognising that patients undergoing treatments like angioplasty or coronary revascularisation often continued smoking. Launched in December 2003 for this group, it later expanded nationwide through awareness campaigns.[13]

Uruguay's 2008 Comprehensive Tobacco Control Law (Law No. 18.256 (https://www.impo.com.uy/bases/leyes/18256-2008.) required all primary care providers, public or private, to include tobacco dependence diagnosis and treatment as a basic service. In 2009, the Ministry of Public Health (MSP) and NRF issued national guidelines including training, nicotine gum and free bupropion to institutions with cessation programmes and minimal or no copayments.[13] Providers without NRF agreements had to offer services but could charge copayments.

The TTP of the NRF is one of the few large-scale cessation initiatives that operates within a universal health system and systematically monitors patient outcomes. Unlike many cessation programmes in high-income countries, which rely primarily on pharmacotherapy delivery or digital services, the TTP integrates behavioural counselling with pharmacological treatment, allowing standardised follow-up across healthcare providers. The existence of a single national programme also enables the estimation of transition probabilities based on real-world data, which is uncommon in economic evaluations of smoking cessation.

Operationally, the TTP combines pharmacological treatment (bupropion and nicotine gum) with structured counselling delivered by trained health professionals. Patients are typically offered at least three counselling visits during treatment initiation. Adherence to follow-up is strongly associated with success: 55% of participants who attend ≥3 sessions achieve point-prevalence abstinence at 12 months, compared with 10–14% among those with fewer visits.[14] This feature makes the programme particularly valuable for evaluating long-term outcomes, since many cessation interventions lack systematic follow-up.

The NRF monitors annual cohorts using surveys stratified by gender, provider type, medication use and number of counselling visits. Data from the 2016–2017 cohort (latest available) show follow-up visits are key to cessation: 55% of those attending three or more visits achieved point prevalence abstinence (Point prevalence abstinence is defined as the percentage of patients who achieved at least a 7-day abstinence period at any time during tobacco cessation treatment.) in the first year, versus 14% among those with fewer visits. 6-month abstinence was 30% versus 17%, and 12-month abstinence was 27% versus 10%.[14]

Results also differed by treatment site. Participants in 'internal' NRF units showed higher abstinence rates across all measures than those in 'external' units. Point prevalence at 12 months was 44% versus 36%, 6-month abstinence was 31% versus 21% and 12-month abstinence was 25% versus 16%, respectively.[14]

Despite its strong performance, the current pharmacological options are limited to bupropion and nicotine gum. Nicotine patches are not currently financed by the programme (although available in the market) and cytisine is not yet available in the country as a treatment option (as it depends on a pharma company being willing and subsequently applying to bring in the medication into the country). Both therapies have shown superior or comparable effectiveness in the international literature and may particularly benefit highly dependent people who smoke. Given that Uruguay already finances the treatment of tobacco-attributable diseases—including cancer, COPD and cardiovascular events—the question for policymakers is not whether to pay, but when. Investing earlier through effective cessation may reduce downstream treatment expenditure and productivity losses.

Taken together, Uruguay represents a unique setting to evaluate smoking cessation interventions: (1) tobacco control policies are already mature and comprehensive, reducing confounding from concurrent policy changes; (2) the TTP provides real-world cessation probabilities; and (3) the health system internalises the economic consequences of continued smoking. These characteristics allow for a cost-effectiveness analysis that directly informs financing decisions, something that is rarely possible in countries without universal treatment coverage.

DATA AND METHODOLOGY

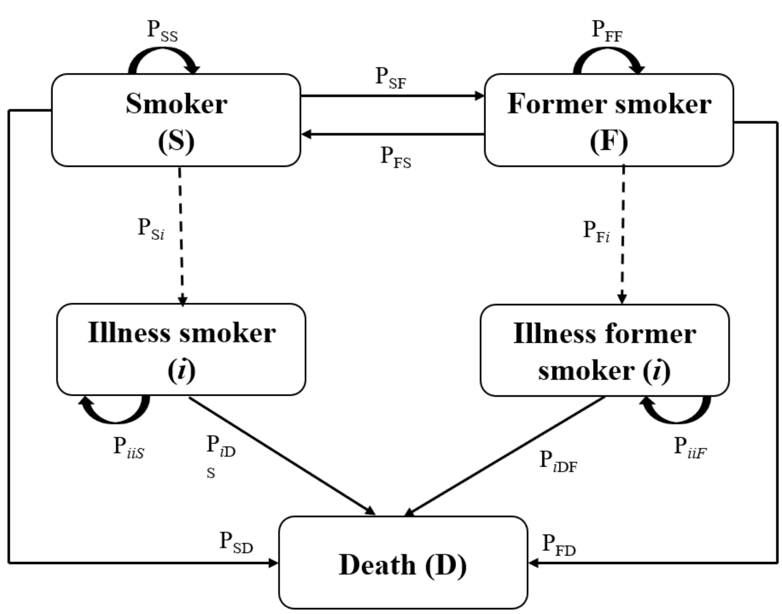
To conduct the economic evaluation of the TTP, we carried out a cost-effectiveness analysis based on Markov models with five mutually exclusive main states: undiagnosed people who smoke, undiagnosed people who have quit smoking, diagnosed people who smoke (with one of the seven tobacco-related illnesses), diagnosed people who have quit smoking and dead (the latter being an absorbing state).[2 3 15 16] We follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 updated guidance checklist to report economic evaluations (complete checklist provided as online supplemental material).[17] This study was not conducted using patients or a clinical trial, only using government or public information only. Thus, ethical approval was not needed.

As expected, the TTP cohort is not representative of all people who smoke in Uruguay, as participants are treatment-seeking individuals, often with higher nicotine dependence and comorbidities. Thus, estimated cessation probabilities may differ from population averages. We explicitly incorporate this limitation in interpreting the results.

To simulate the process of quitting smoking, we used a stratified sample from the latest cohort of TTP people who smoke in 2016–2017 (provided by the NRF, through liaising with their former and current directors of the institution).[14] The sample consisted of 57% women, with an average age of 48 years. Nearly half of the participants lived in the capital, one-fifth had tertiary education and about one-third had public health coverage. Participants began smoking at an average age of 16 years and smoked about 20 cigarettes per day when entering the TTP.

Figure 1 presents the Markov model used, which includes transition probabilities between states for seven smoking-related diseases. The transition probabilities (P_{SS}, P_{SF}, P_{FS}, P_{FF}) are based on data from the NRF's 2016–2017 cohort and vary by gender and age. Probabilities were calculated based on sustained abstinence at 6 and 12 months.

The model operates in 6-month cycles, during which participants can move between states: people who smoke,



P_{SS}: Smoker who remains a smoker
P_{FF}: Former smoker who remains a former smoker
P_{SF}: Cessation rate
P_{FS}: Relapse rate
P_{SD}: Mortality rate among smokers excluding the 7 illnesses
P_{FD}: Mortality rate among former smokers excluding the 7 illnesses
P_{Si}: Illness incidence rate i for smokers
P_{Fi}: Illness incidence rate i for former smokers
P_{iiS}: Smoker living with illness i
P_{iiF}: Former smoker living with illness i
P_{iDS}: Mortality rate for smoker with illness i
P_{iDF}: Mortality rate for former smoker with illness i

Figure 1 Structure of the Markov model used to simulate smoking cessation trajectories and associated health and economic outcomes. Individuals enter the model as smokers and may transition between mutually exclusive health states representing smoking status (current smoker or former smoker), diagnosis of tobacco-related disease, and death (absorbing state). Transitions occur in 6-month cycles over the model time horizon, with probabilities varying by age and sex. Intervention scenarios affect cessation and relapse probabilities but not disease-specific transition structures. Source: based on.[2 3 56]

people who have quit smoking and death. Both people who smoke and people who have quit smoking are at risk of developing the following diseases associated with active smoking (Due to the lack of information regarding second-hand smoke exposure, smoke-related illnesses will not be considered in the analysis. Peripheral artery disease, which primarily affects heavy people who smoke, is also not considered because it is not reported in the MSP mortality tables.): lip, oral cavity and pharynx cancer (C00-C14) (The codes correspond to the International Classification of Diseases.), oesophageal cancer (C15), laryngeal cancer (C32), trachea, bronchus and lung cancer (C33, C34), ischaemic heart diseases (I20-I25), cerebrovascular diseases (I60-I69), chronic lower respiratory diseases (J40-J47).

Mortality probabilities and prevalence for each disease were estimated following the methodology proposed by Flack *et al*,[15] adjusting the mortality tables of Doll *et al*[18] by disease. To calculate prevalence (P_{Si} and P_{Fi}) and disease-specific mortality (P_{iDS} and P_{iDF}), we used mortality statistics from the MSP and relative risk ratios from previous studies.[15 19 20] Mortality from causes not associated with smoking was assumed to be equal for people who smoke and people who have quit smoking (P_{SD} and P_{FD}), based on MSP data.

In our model and following,[3] people who have quit smoking were assigned a constant relative risk of morbidity and mortality compared with people who smoke. We did not stratify risks by time since quitting due to data limitations. This simplifying assumption likely underestimates the long-term health benefits of sustained abstinence, as epidemiological evidence shows that morbidity and mortality risks decline progressively with increasing years since cessation.[8 9]

The model's time horizon spans from age 18 (legal adulthood in Uruguay) until the life expectancy: 74 years for men and 81 years for women, allowing us to include a long-term perspective from an individual point of view (INE, Esperanza de vida al nacer por sexo | Tabla | Observatorio Territorio Uruguay.). Participants transition between states with age-increasing probabilities. We performed a simulation of a 10 000 individual cohort of people who smoke for each scenario, allowing estimation of cumulative costs and benefits, measured in YLL for each alternative. YLLs are calculated by multiplying the number of deaths by the standard life expectancy at the age of death. The results shown in this study are presented based on those cohort simulations.

We evaluated five policy alternatives:

1. No intervention: Based on transition probabilities from the 2018 National Drug Consumption Survey.[21] Since in this survey the P_{SF} transition is nested within the P_{SS}, we use the transition that arises from the NRF for this case. This is the base case used for the comparisons with the sensitivity analysis (cases two to five).
2. Current NRF TTP: Includes nicotine gum and bupropion (It is estimated that 30% of patients have contraindications to bupropion use. This percentage has already been included in the medication expenditure data from the current NRF TTP. The average duration of medication use is 60 days.).
3. Expanded NRF TTP: Includes nicotine patches for patients with severe nicotine dependence (Fagerström test score of 7 or higher).
4. Future programme: Combines cytisine and counselling[22–24] without changes in mortality rates compared with alternatives 2 and 3.[25]
5. Future programme with a 14% reduction in mortality from tobacco-related diseases, based on a lung cancer simulation model .[26]

The decision to include these alternatives is based on priorities of the NRF and does not aim to be exhaustive from a theoretical point of view. Although mCessation or quitlines could be included as alternatives and are part of prior population-level analyses in low- and middle-income countries,[27] we decided, in discussion with NRF authorities, to not include these given the lack of assigned costs within the Uruguayan health system, not allowing us to have a comparable and consistent modelling against the alternatives defined above. We did, however, include psychological counselling as it is part of the current NRF TTP (alternatives 2 and 3). There is consensus in the literature that smoking cessation programmes should combine psychosocial interventions with pharmacological therapies. First-line pharmacotherapies with proven efficacy and safety include varenicline, bupropion and NRT (patches, gum); second-line drugs like nortriptyline and clonidine are used in special cases due to greater health risks.[28] Cytisine, though not yet approved in the USA or much of Europe, is considered first-line and included in guidelines in Eastern Europe and Germany.[28–30] Although there is strong long-term evidence on the usage and efficacy of varenicline,[31–33] we did not include it as an alternative based on local health policy criteria and relative costs, given that cytisine is the pharmacological alternative that the NRF was considering as a cost-effective substitute, and for which recent evidence of effectiveness is also robust.

The current NRF TTP provides nicotine gum, bupropion and counselling. To estimate programme costs (medication and staff salaries), we used annual data from the NRF and Hospital de Clínicas (an internal unit in Montevideo). The annual cost per patient was calculated as the weighted sum of salaries and medications based on the NRF's 2016–2017 cohort.

In policy alternative 3, we add nicotine patches to NRT. Based on Esteves *et al*,[14] about 30% of TTP participants had severe nicotine dependence per the Fagerström test.[34 35] For these participants, we considered a standard three-cycle patch treatment (21, 14 and 7 mg over successive 21-day periods). As patches are not available in Uruguay, average prices from USA and UK pharmacies were used.

For the future cytisine interventions, we propose combining pharmacological and psychological support, using the current TTP's counselling structure, which is ideal for resource-limited systems. The classic cytisine regimen is a 25-day tapering schedule of 1–3 days of one tablet every 2 hours (maximum six per day), decreasing to five tablets per day from days 4–12, 13–16 to four tablets per day, 17–20 to three tablets per day and 21–25 to one or two tablets per day. Newer studies like the RAUORA trial[36] and protocols in Germany and the UK explore extended 12-week regimens, especially for highly dependent patients. We used the 3-month regimen to represent a maximum-benefit scenario. Because cytisine reduces relapse rates, we assumed a zero probability of reverting to smoking once participants quit. International prices were used, as cytisine is not yet available in Uruguay.

Although no clinical trials directly show mortality reductions from cytisine,[26] using a lung cancer model (CISNET, Cancer Intervention and Surveillance Modelling Network) found interventions could reduce cancer death by 14% with a 10% cessation rate. We included this estimate in our final simulation scenario, applying the 14% reduction to all tobacco-related diseases.

Policy effects were operationalised by modifying the transition probability from people who smoke to people who have quit smoking. Relapse probabilities were held constant across scenarios, given limited evidence on how policies differentially affect relapse.[37–39] In addition, while quitting probabilities were stratified by age and sex based on the TTP cohort, we did not model additional heterogeneity in policy effects by demographic groups, such as race, education or region. This approach ensures comparability across scenarios, but may underestimate benefits if some interventions are more effective in specific subpopulations.

The analysis was conducted from two perspectives:

- Healthcare perspective: only includes treatment costs for smoking-related diseases and the intervention.
- Societal perspective: adds productivity loss costs, calculated based on sick leave days, average hourly wages and employment rates by gender and age. We used the 2017 national averages of sick leave and wage data, assuming a 40-hour workweek and adjusting productivity loss estimates for those employed.

Although a full societal perspective is not adopted (as usually defined), the inclusion of avoided healthcare costs reflects an extended public payer perspective, consistent with NRF decision-making.

The simulations estimate cumulative costs and health outcomes for each alternative over time. In Uruguay, treatment for tobacco-related diseases is covered by either national public insurance, public coverage, private insurance or through the NRF for all residents. The average direct medical costs for treating each tobacco-attributable disease are from.[12] The authors estimated disease treatment costs using microcosting or macrocosting approaches, depending on data availability. For micro-costing, they consulted experts, guidelines and medical records. When data were lacking, they applied disease treatment costs as a percentage of per capita Gross Domestic Product (GDP) from other countries to the target country's GDP. While this method may oversimplify by assuming similar cost-to-GDP relationships and overlooking health system differences, it is considered conservative. The method excludes indirect costs, relies on average or outdated data and likely underestimates costs for countries like Uruguay with stronger health systems—making the findings a minimum scenario.

As an outcome indicator, the ICER was calculated as the difference in costs divided by the difference in effectiveness between alternatives. The ICER indicates whether the additional benefits of a new intervention justify its extra costs, helping to guide healthcare resource allocation and support value-for-money decisions. The ICER and its CIs are generated through 1000 bootstrap replications, presenting the average value as well as 95% CIs.

$$\text{ICER} = \frac{\text{Cost intervention} - \text{Cost alternative}}{\text{YLL intervention} - \text{YLL alternative}} \qquad (1)$$

To indicate the model's probabilistic response to different cost-effectiveness thresholds, we plotted the cost-effectiveness acceptability curve (CEAC). As the willingness to pay thresholds, we include US$1.675, which is Uruguay's expenses in health per capita, the ICER lower and upper thresholds (2017 values, US$1747 and US$3685) from a nicotine replacement therapy+bupropion intervention,[40] as well as the GDP per capita and half of this measure (US$19 250, current US$).[41 42] We also calculate cost-effectiveness acceptability curves which compare the no programme alternative against the other four options.[43 44]

We applied a 3% discount rate to future costs and benefits[3 45] and a 5% as a sensitivity analysis (the rounded annual inflation rate for Uruguay, for year 2024). Two other one-way sensitivity analyses include changes in the prices of nicotine patches for Argentinian values, to reflect regional costs and to assess the robustness of results to uncertainty around the assumption in policy alternative 5, we explored an alternative mortality risk reduction (10%), instead of the 14% originally used.[8 9 46] The values of these sensitivity analyses are found in the online supplemental appendix.

Tables 1 and 2 summarise the varied information sources used to define the variables and include, whenever possible, summary statistics (mean, 95% CIs or SD). A summary section of the model formulation can be found in the online supplemental appendix, as well as additional and more detailed information not found in tables 1 and 2 (see online supplemental Tables A2 to A5).

Patient and public involvement

Patients and the public were not involved in the design, conduction, reporting and dissemination plans of our research.

Table 1 Individual characteristics and costs

	Source	Values
Socioeconomic characteristics (by age group and sex)		
Employment rate	Household survey, Statistical National Institute	Female (age cohort, wage): 18–19: 0.303, 20–24: 0.582, 25–29: 0.786, 30–34: 0.825, 35–39: 0.846, 40–44: 0.846, 45–49: 0.837, 50–54: 0.803, 55–59: 0.727, 60+: 0.168 (mean: 0.672, 95% CI 0.497 to 0.848) Male (age cohort, wage): 18–19: 0.356, 20–24: 0.609, 25–29: 0.799, 30–34: 0.847, 35–39: 0.866, 40–44: 0.864, 45–49: 0.857, 50–54: 0.819, 55–59: 0.752, 60+: 0.336 (mean: 0.711, 95% CI 0.562 to 0.859)
Average hours worked	Assumption	8 hours/day
Average hourly wage	Household survey, Statistical National Institute, in UYU per hour	Female (age cohort, wage): 18–19: 98.4, 20–24: 126.6, 25–29: 164.2, 30–34: 186.2, 35–39: 202.7, 40–44: 210.5, 45–49: 209.2, 50–54: 216.2, 55–59: 229.2, 60+: 186.9 (mean: 183.0, 95% CI 153.1 to 213.0) Male (age cohort, wage): 18–19: 99.4, 20–24: 126.1, 25–29: 163.7, 30–34: 185.2, 35–39: 202.6, 40–44: 211.9, 45–49: 213.1, 50–54: 219.6, 55–59: 232.7, 60+: 230.4 (mean: 188.5, 95% CI 156.0 to 220.9)
Average sick leave days	Banco de Previsión Social (BPS), Uruguay. File #2023-28-1-134648	Online supplemental Table A2. Female: Circulatory (I20–I25, I60–I69), mean=50.9, 95% CI 30.9 to 70.9. Respiratory (J40–J47), mean=10.9, 95% CI 8.1 to 13.7 Tumours (C00–C14, C15, C32–C34), mean=114.3, 95% CI 92.0 to 136.6 Male: Circulatory (I20–I25, I60–I69), mean=55.5, 95% CI 29.3 to 81.7 Respiratory (J40–J47), mean=11.6, 95% CI 6.9 to 16.3 Tumours (C00–C14, C15, C32–C34), mean=124.1, 95% CI 110.7 to 137.5
Characteristics associated with smoking		
NRF transition probabilities	NRF tobacco consumption survey, cohort 2016–2017	Calculated based on confidential data from NRF can be provided by request
Cytisine transition probabilities	24	p_{ss}=0.30; p_{sf}=0.70; p_{fs}=0; p_{ff}=1
Costs		
Sickness benefit	Banco de Previsión Social, Uruguay.	70% of taxable income, payment after 4 days of sick leave https://www.bps.gub.uy/4774/subsidio-por-enfermedad.html
Treatment costs for smoking-related diseases	[12], in UYU per year, fixed values	Cancers: pharynx=22 993; oesophagus=26 749; larynx=26 810; lung=42 742 Heart: cerebrovascular=4442 ischaemic=4024 Respiratory: COPD=1799
Cost of NRF cessation programme (including medical and medication costs)	Confidential data from the NRF and Hospital de Clínicas, fixed values	UYU 3960 (cost per patient, per admission)
Cost of cytisine	Average international pharmacy prices in the USA and the UK, in UYU per 10 weeks, fixed values	UYU 19 800 (cost per patient, per treatment)
Cost of nicotine patches	Average international pharmacy prices in the USA and the UK, in UYU per 10 weeks, fixed values	UYU 5400 (cost per patient, per treatment)

CEAC, Cost Effectiveness Acceptability Curve; COPD, chronic obstructive pulmonary disease; NRF, National Resources Fund; RR, Risk Ratios; UYU, Uruguayan Pesos; YLL, Years of Life Lost.

Table 2 Prevalence of tobacco-attributable diseases

	Source	Values
Neoplasms	MSP vital statistics (ICD code)	
Lip, oral cavity and pharynx cancer	C00-C14	Online supplemental Table A4. We assume prevalence for 18–19 cohort is the same as 20–24. Female (mean, SD): Lip, oral cavity and pharynx cancer (0.00222, 0.00315) Oesophageal cancer (0.00422, 0.00535) Laryngeal cancer (0.00078, 0.00164) Trachea, bronchus and lung cancer (0.02678, 0.03443) Male (mean, SD): Lip, oral cavity and pharynx cancer (0.02800, 0.06599) Oesophageal cancer (0.04667, 0.12342) Laryngeal cancer (0.03000, 0.07746) Trachea, bronchus and lung cancer (0.05256, 0.06794)
Oesophageal cancer	C15	
Laryngeal cancer	C32	
Trachea, bronchus and lung cancer	C33, C34	
Cardiovascular illnesses		
Cerebrovascular diseases	I60-I69	Online supplemental Table A4. We assume prevalence for 18–19 cohort is the same as 20–24. Female (mean, SD): Ischaemic heart diseases (0.02611, 0.02856) Cerebrovascular diseases (0.04411, 0.03126) Male (mean, SD): Ischaemic heart diseases (0.07211, 0.09414) Cerebrovascular diseases (0.05222, 0.08628)
Ischaemic heart diseases	I20-I25	
Respiratory illnesses		
Chronic lower respiratory diseases (COPD)	J40-J47	Online supplemental Table A4. We assume prevalence for 18–19 cohort is the same as 20–24. Female (mean, SD): Chronic lower respiratory diseases (0.01856, 0.01512) Male (mean, SD): Chronic lower respiratory diseases (0.03478, 0.06808)
Risk ratios (by illness)	[19 20 57 58], fixed values	We assume the RR of people who smoke=1 for all diseases, then vary the people who have quit smoking RRs. Cancers: pharynx=0.709; oesophagus=0.709; larynx=0.709; lung=0.44 (male) per 0.21 (female) Heart: cerebrovascular=0.497; ischaemic=0.173 Respiratory: COPD=0.573

Continued

Table 2 Continued

	Source	Values
Prevalence of smoking, non-smoking and quitting smoking by age and sex	2018 National Survey on Drug Use in the General Population (JND)	Online supplemental Table A6. Female (mean, SD): People who smoke (0.0373, 0.0569) People who have quit smoking (0.0139, 0.0176) Male (mean, SD): People who smoke (0.0803, 0.1371) People who have quit smoking (0.0358, 0.0616)
Calculated probability of dying from disease, age and sex (for people who smoke+people who have quit smoking)	Constructed based on MSP vital statistics using[15]	Online supplemental Table A5. We assume prevalence for 18–19 cohort is the same as 20–24. Female (mean, SD): People who smoke (27.38, 7.74) People who have quit smoking (57.36, 15.22) Male (mean, SD): People who smoke (37.70, 10.38) People who have quit smoking (66.58, 17.20)
Mortality tables for smoking-related diseases	18	Online supplemental Table A3. We assume prevalence for 18–19, 20–24, 25–29 and 30–34 is the same as 35–39. People who smoke: mean: 58/100 000, 95% CI 15.9 to 131.8 People who have quit smoking: mean: 44.4/100 000, 95% CI 16.1 to 104.9

COPD, chronic obstructive pulmonary disease; GDP, Gross Domestic Product; ICD, International Classification of Disease; MSP, Ministry of Public Health; PV, Present Value; RR, Risk Ratios.

Table 3 Average years of life lost (accrued over 10 000 individual simulations)

	Male		Female		Total	
	Average change in YLL, %	Difference in per capita YLL	Average change in YLL, %	Difference in per capita YLL	Average change in YLL, %	Difference in per capita YLL
Comparing with no intervention (alternative 1)						
Current NRF TTP vs no intervention* (2 vs 1)	−1.4	−0.34	−12.0	−3.50	−7.2	−3.84
Current NRF TTP+patches vs no intervention* (3 vs 1)	−1.4	−0.34	−12.0	−3.50	−7.2	−3.84
Cytisine no mortality adjustment vs no intervention (4 vs 1)	−4.0	−0.96	−16.5	−4.82	−10.9	−5.78
Cytisine with mortality adjustment vs no intervention (5 vs 1)	−6.2	−1.48	−21.4	−6.26	−14.6	−7.74
Comparing with NRF TTP (alternative 2)						
Current NRF TTP+patches vs current NRF TTP (3 vs 2)	0.0	0.00	0.0	0.00	0.0	0.00
Cytisine no mortality adjustment vs current NRF TTP (4 vs 2)	−2.6	−0.62	−5.1	−1.32	−3.9	−1.94
Cytisine with mortality adjustment vs current NRF TTP (5 vs 2)	−4.8	−1.14	−3.2	−0.76	−4.0	−1.90

*The YLL for alternatives 2 and 3 are the same, as they use identical transition probabilities, differing only in programme costs.
NRF, National Resources Fund; TPP, Tobacco Treatment Programme; YLL, years of life lost.

RESULTS

The results in table 3 show that all interventions reduce the YLL compared with no intervention (accrued from the 10 000 simulations). This means that by itself, any tobacco cessation intervention is policy relevant (meaning, better than doing nothing at all). When comparing to no programme, and as expected, the greatest reduction is observed with the cytisine intervention including adjusted mortality (5 vs 1), achieving a 14.6% reduction in total YLL and 7.74 years per capita. This effect is more pronounced among women, with a 21.4% decrease in YLL versus 6.2% among men. Accrued YLL values used for these calculations, and for the cohort of 10 000 simulated individuals, can be found in online supplemental Appendix Table A1.

For policy purposes, the relevant comparison is the current NRF TTP (the institutionally relevant baseline). When comparing this future intervention to the current NRF TTP (5 vs 2 and 4 vs 2), the reduction in YLL when using cytisine (with and without mortality adjustment) is 4.0%, with improvements both in men (−4.8%, −2.6%) and in women (−3.2%, −5.1%). Because the current TTP already captures a substantial share of achievable health gains, incremental improvements relative to this baseline are necessarily smaller than in a situation with no policy at all. This does not indicate limited effectiveness of these programme but rather reflects the maturity of Uruguay's tobacco control policies. This means that on the total, we see less YLLs.

The significant gender difference in effectiveness suggests women benefit more from smoking cessation interventions. In absolute terms, women also gain in total more life years per capita in most scenarios. This disparity by gender could stem from women's higher treatment adherence,[47] greater healthcare engagement and lower cigarette consumption—averaging 10.6/day versus men's 12.9 in a 30-day period[21]—which may facilitate quitting.[48] Women also show greater readiness to quit, often tied to reproductive life stages,[49] and respond better to psychological and motivational interventions, key components of the TTP.[50] These factors help explain why smoking cessation programmes could have a stronger impact on female YLL.

Table 4 shows the ICER results in US$ per YLL (US$ per YLL) from the bootstrapping exercise (1000 replications) based on the 10 000 created simulations for each policy alternative. We examine the ICERs from the two perspectives, health (only the cost of treating smoking-related diseases is considered) and societal (adds productivity loss costs).

Table 4 Incremental cost-effectiveness ratios, US$ per YLL (10 000 bootstrapped replications)

	Health perspective			Societal perspective		
	Male	Female	Total	Male	Female	Total
	Comparing with no intervention (alternative 1)					
Current NRF TTP vs no intervention (2 vs 1)	1336.2 (1114.5 to 1557.9)	9999.7 (8076.5 to 12 545.7)	4852.1 (4189.3 to 5582.3)	1475.2 (1243.4 to 1717.2)	10 960 (8883.6 to 13 713.5)	5324.6 (4617.8 to 6102.8)
Current NRF TTP+patches vs no intervention (3 vs 1)	1201.9 (999.4 to 1438.1)	10 333.2 (8334.5 to 13 053)	4795.8 (4133.3 to 5529.6)	1340.1 (1109.1 to 1571.1)	11 323.6 (9171.3 to 14 295.4)	5269.4 (4560.2 to 6062.1)
Cytisine no mortality adjustment vs no intervention (4 vs 1)	1824.4 (1675.4 to 1993.7)	7394.5 (6322.5 to 8652.8)	4378.2 (3962.4 to 4829.4)	2022.4 (1861.4 to 2203.8)	8123.0 (6969.0 to 9482.1)	4819.4 (4373.2 to 5303.2)
Cytisine with mortality adjustment vs no intervention (5 vs 1)	1469.5 (1346.5 to 1592.5)	5475.8 (4783.9 to 6268.7)	3391.2 (3085.9 to 3728.8)	1629.1 (1504.3 to 1775.7)	6015.6 (5273.4 to 6866.0)	3733.2 (3407.8 to 4088.2)
	Comparing with NRF TTP (alternative 2)					
Cytisine no mortality adjustment vs current NRF TTP (4 vs 2)	1038 (930.3 to 1146.5)	−2883.6 (−3882.2 to −1933.9)	3278 (2505 to 4051.1)	1156.7 (1038.9 to 1274.4)	−3200 (−4247.7 to −2152.4)	3644.4 (2789.2 to 4499.6)
Cytisine with mortality adjustment vs current NRF TTP (5 vs 2)	823.5 (741.3 to 905.7)	−36 961.5* (−2 976 792 to 2 902 869)	1711 (1463.2 to 1958.8)	918.2 (828.6 to 1007.7)	−41 002* (−3 305 803 to 3 223 799)	1902.8 (1630.5 to 2175.2)

CIs at 95% in brackets. Values exchanged from UYU to US$ at a rate of US$1 to UYU 28.6. We do not show comparison 3 versus 2 given that the gains in YLL are almost zero from introducing patches to the current NRF TTP, which inflates the ICER values.
*Note that comparison 5 versus 2 for women shows an inflated ICER as YLL average gains are close to 0, thus making it on the average cost-effective but not effective in health gains for women. This is explained carefully in-text.
ICER, incremental cost-effectiveness ratio; NRF, National Resources Fund; TTP, Tobacco Treatment Programme; YLL, years of life lost.

We first compare the interventions against no intervention. We find that all four alternative interventions are cost-effective from both health and societal perspectives. That is, for Uruguay, tobacco cessation programmes are cost-effective regardless of the type of programme evaluated. From a health perspective, the most cost-effective intervention compared with no intervention is cytisine with adjusted mortality (5 vs 1), with an average ICER of US$3391 per YLL (3085.9 to 3728.8), followed by cytisine without adjusted mortality (4 vs 1). Compared with the international literature, these values are consistent with studies in other countries.[8 51] We find similar results in the ICERs from a societal perspective: for example, the cytisine programme (4 vs 1) has ICER of US$4819.4 per YLL (4373.2 to 5303.2).

In all cases, cost-effectiveness is higher in women than in men, reflecting the greater impact on YLL reduction and the lower investment required just from incorporating a tobacco cessation programme into tobacco reduction policies. Compared with no intervention, from a health perspective, the current NRF TTP (2 vs 1) averts US$1336 per YLL (1114.5 to 1557.9) for men, while for women this is almost US$10 000 per YLL (8076.5 to 12 545.7), a large difference in cost-effectiveness. Similar results are shown comparing to the expanded NRF TTP, which includes nicotine patches (3 vs 1). From a societal perspective, mortality-adjusted cytisine remains the most cost-effective intervention relative to no intervention (5 vs 1), at US$1629 per YLL in men and US$6016 per YLL in women. Across one-way scenario sensitivity analyses (5% discount rate; alternative regional pricing for nicotine patches; and a more conservative 10% mortality reduction for cytisine), the main conclusions remain unchanged: cytisine remains cost-effective (and in some subgroup comparisons cost-saving), whereas the incremental value of adding patches is highly sensitive to their unit price and can yield inflated ICERs when incremental YLL gains are close to zero. Detailed results are reported in online supplemental Appendix Tables A6–A8.

In all comparisons, cost-effectiveness from a societal perspective is considerably higher in women than men, suggesting that the benefits in YLL reduction from establishing a tobacco cessation programme are greater in women. When comparing the current NRF TTP versus no intervention (2 vs 1), the cost per YLL avoided is US$1475 per YLL (1243.4 to 1717.2) in men and only US$10 960 per YLL (8883.6 to 13 713.5) in women, reinforcing the pattern of greater cost-effectiveness for women.

As our relevant question is how to extend and improve existing cessation policies, our results are also interpreted relative to the current NRF TTP. Compared with the current NRF TTP, both alternatives are cost-effective on the total, with, for example, cytisine (4 vs 2), yielding an ICER of US$3278 per YLL (2505 to 4051.1) from a health perspective and an ICER of US$3644.4 per YLL (2789.2 to 4499.6) from a societal perspective.

However, when incremental health gains are evaluated relative to an already effective programme, such as the current NRF TTP, ICERs may become unstable or difficult to interpret, particularly in subgroup analyses, such as gender (in our case[52 53]). In such cases, results are better interpreted using incremental costs and effects, cost-effectiveness acceptability curves rather than point ICER estimates may provide more transparent and decision-relevant evidence for policymakers.[54 55]

As an example, using the health perspective, in the case of men, the cytisine versus current NRF TTP comparison yields cost savings on the average (average Δcost=–165 887 (−178 570.4 to −153 203.9)), and reduces YLL (average Δeffectiveness is −7.03 (−7.46 to −6.60)), being dominant in both effectiveness and cost savings (ICER from 1000 bootstrapped replications is US$1038 per YLL (930.3 to 1146.5)). However, for women, we find a different story, where we see inflated ICERs. We find that on average, the Δeffectiveness for women, health perspective is less than 1 (0.13 (−0.39 to 0.64)), making the ICER explode. Thus, it is dominant in savings, with an average Δcost=–36 961.5 (−2 975 321 to 2 901 398), but not in effectiveness, with incremental effects on effectiveness being statistically indistinguishable from zero (p=0.627 for test of Δeffectiveness=0). A similar conclusion can be discussed in the case of the societal perspective.

In addition, table 5 reports the present value of per capita costs. The costs of no intervention are shown to be high from both perspectives, health and societal. Cytisine is the least costly alternative from both perspectives (health and societal), reflecting the positive impact on smoking cessation and the labour market of this tobacco cessation programme alternative.

Lastly, comparing the CEAC across the different scenarios, all of the alternative scenarios (2–5) across both health and society perspectives are 100% cost-effective using the traditional GDP per capita and 0.5×GDP per capita thresholds (figures 2 and 3).

DISCUSSION

From a policy perspective, our results suggest that incorporating cytisine (the medication prioritised by the NRF) into the national formulary and integrating it into the current TTP could generate health gains while reducing long-term costs. Beyond medication choice, these findings reinforce the value of structured follow-up and behavioural counselling, both central components of the TTP. Strengthening referral pathways from primary care to cessation services, reducing administrative barriers and promoting proactive outreach (with particular focus on women) would further increase programme effectiveness. Although not included in our study due to policy objectives of the NRF, the inclusion of varenicline, which has also robust evidence of its efficacy for tobacco cessation, could also bring high benefits, as it has the strongest and most consistent rates of long-term tobacco cessation among pharmacological treatments.

The analysis also shows substantial heterogeneity by sex: women benefit more from cessation in terms of YLL

Table 5 Average present value of costs (per capita) by alternative and perspective, in US$

	Male	Female	Average
Health perspective			
No intervention	12885.5 (22 856.0)	32122.1 (107 269.4)	23663.8 (82 253.0)
Current NRF TTP	7416.5 (14 727.0)	6259.7 (20 234.2)	6768.3 (18 029.5)
Current NRF TTP+patches	7554.3 (14 775.7)	6570.8 (20 345.6)	7003.2 (18 114.6)
Cytisine no mortality adjustment	1883.6 (4344.7)	1250.0 (739.0)	1528.6 (2950.3)
Cytisine with mortality adjustment	1980.2 (4705.6)	1254.0 (743.7)	1573.3 (3189.8)
Societal perspective			
No intervention	14139.5 (24 392.7)	35157.0 (11 1490.1)	25915.6 (85 641.3)
Current NRF TTP	8108.5 (15 681.8)	6799.1 (21 194.8)	7374.8 (18 979.4)
Current NRF TTP+patches	8246.4 (15 734.6)	7170.1 (21 310.5)	7609.7 (19 068.2)
Cytisine no mortality adjustment	1930.1 (4550.7)	1250.8 (743.9)	1549.5 (3086.8)
Cytisine with mortality adjustment	2033.8 (4930.7)	1254.8 (748.6)	1597.3 (3339.5)

SD in parentheses. Average PV calculations come from 10000 simulations at 3% annual interest. Values exchanged from UYU to US$ at a rate of US$1 to UYU 28.65.
NRF, National Resources Fund; PV, Present Value; TTP, Tobacco Treatment Programme; UYU, Uruguayan Pesos.

averted and generate lower costs per YLL saved. This highlights an opportunity to design targeted communication and outreach strategies, especially considering that smoking prevalence in Uruguay has declined more slowly among women. Prioritising women in cessation outreach could improve both efficiency and equity.

In addition, the decision to use YLLs, which captures averted mortality, instead of QALYs or healthy life years (HLYs), which captures averted morbidity, was based on the availability and robustness of local data for tobacco-attributable mortality, and to align this study with previous burden-of-disease exercises used in Uruguay to inform policy. We nevertheless acknowledge that this measure underestimates total benefits by not capturing avoided morbidity, as the burden of tobacco morbidity is immense and translates directly into economic savings which are not measured directly by YLLs. Using QALYs or HLYs would increase the effectiveness results even further, especially in the case of cytisine (alternatives 4 and 5). Thus, this study's reliance on YLL, while policy-aligned, means that the true overall return on investment of tobacco control policies is conservatively estimated. There is also the need for future data collection efforts in Uruguay to specifically capture health utility and disability weights necessary to calculate the morbidity component.

ICERs become unstable in sex-stratified comparisons where incremental health effects are close to zero, particularly when comparing cytisine with the current cessation programme among women. In such cases, large or inflated ICER values reflect mathematical properties of the ratio rather than unfavourable outcomes, as seen by the other group of measures included in this study (such as CEACs, costs and accrued YLLs), and interpretation should rely primarily on incremental costs, incremental effects and probabilistic analyses.

In terms of risk stratification within the model, would this type of analysis require introducing additional health states or time since quit–specific transition probabilities, for which consistent local data are not available. Applying values from external cohorts would necessitate strong assumptions regarding their transferability to the Uruguayan context and to a treatment-seeking population. The effect of not using this approach is to underestimate the long-term health gains associated with sustained abstinence. Consequently, our effectiveness and cost-effectiveness estimates—particularly for more effective interventions such as cytisine—should be interpreted as conservative.

Lastly, the available data does not allow us to construct reliable sampling weights that would adequately transform the current, treatment-seeking NRF TTP cohort into a population representative sample, which hinders external validity and does not allow us a weighted-sample sensitivity analysis. Given that treatment-seeking

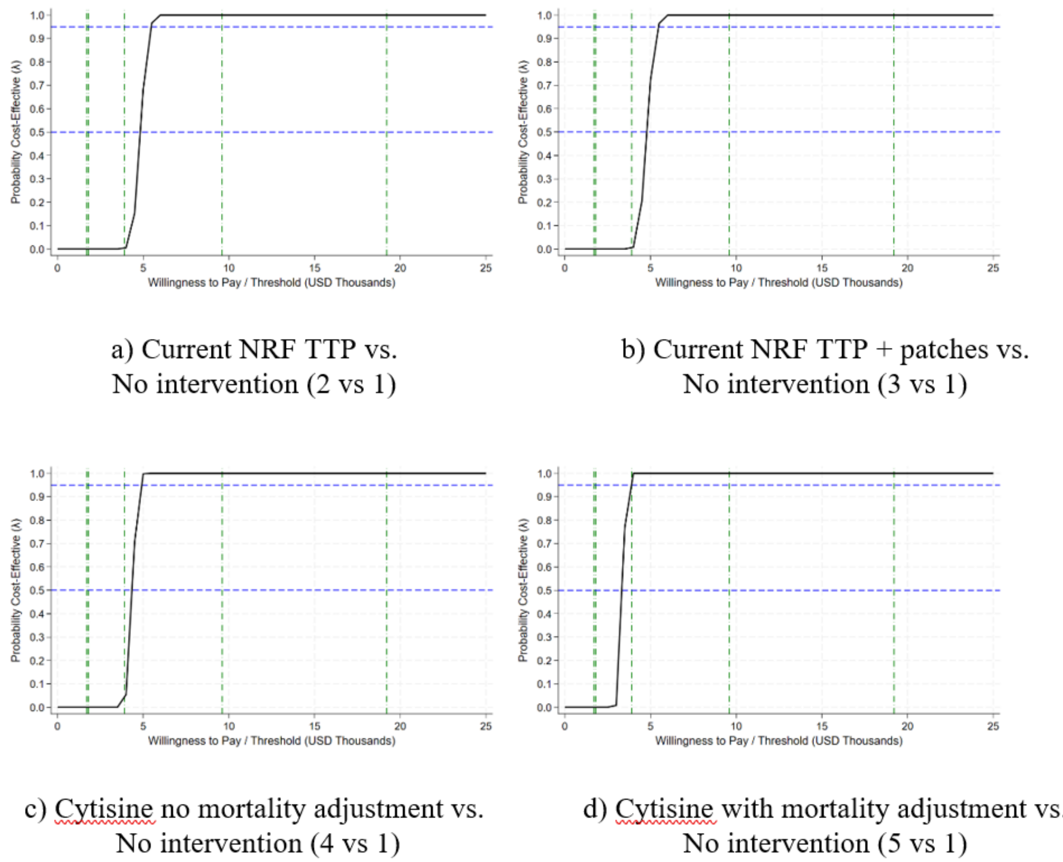


Figure 2 Cost-effectiveness acceptability curve—health perspective.
The CEAC shows the probability that the different alternatives for tobacco cessation programmes are cost-effective (from a health perspective) compared with no intervention, using a range of values for the maximum acceptable ceiling ratio (λ). Thresholds from left to right in thousand US$: 1.7=country expenses in health per capita, 1.8=lower threshold in 2017 values from,[40] 3.9=upper threshold in 2017 values from,[40] 9.6=0.5×GDP per capita, 2017 (World Bank), 19.2=1×GDP per capita, 2017 (World Bank). Horizontal dotted lines represent 50% and 95% probabilities. No image enhancement was performed in each subfigure. Four figures were put together based on the CEAC results for each scenario comparison. CEAC, cost-effectiveness acceptability curve; NRF, National Resources Fund; TTP, Tobacco Treatment Programme.

individuals tend to have higher dependence and comorbidity profiles, our analysis is likely to yield conservative estimates of effectiveness relative to the general smoking population.

Although these limitations imply that our results should be interpreted with caution, the direction of the potential biases suggests that the benefits of the interventions—particularly cytisine—may be underestimated. Therefore, our conclusions are conservative and robust for use in policy design.

Compared with existing studies, a key strength of this analysis is the use of real-world transition probabilities from a national cessation programme operating within a mature tobacco control environment, rather than relying solely on international or trial-based parameters. Unlike most economic evaluations—which are conducted in settings where taxation and regulatory policies are still evolving—this study assesses cessation strategies where the marginal returns to regulation are largely exhausted, increasing the policy relevance of cessation support. In addition, few studies jointly compare multiple pharmacological options, including cytisine, from both healthcare and societal perspectives using YLL as the main outcome. However, relative to other models, our analysis is limited by the use of a treatment-seeking cohort that is not representative of all people who smoke, potentially affecting external validity and by the assumption of constant post-cessation risk over time, which likely leads to conservative estimates of long-term benefits. As in much of the literature, uncertainty increases when incremental effects are small relative to an already effective baseline programme.

Financing cytisine would be a fiscally responsible decision. Because the health system already absorbs the costs of treating diseases caused by tobacco use—including cancer, COPD and ischaemic heart disease—public funding of effective cessation shifts spending from high-cost treatment of preventable illness toward prevention. In economic terms, the comparison is no longer between 'spending or not spending', but between spending earlier to prevent disease or spending later to treat it.

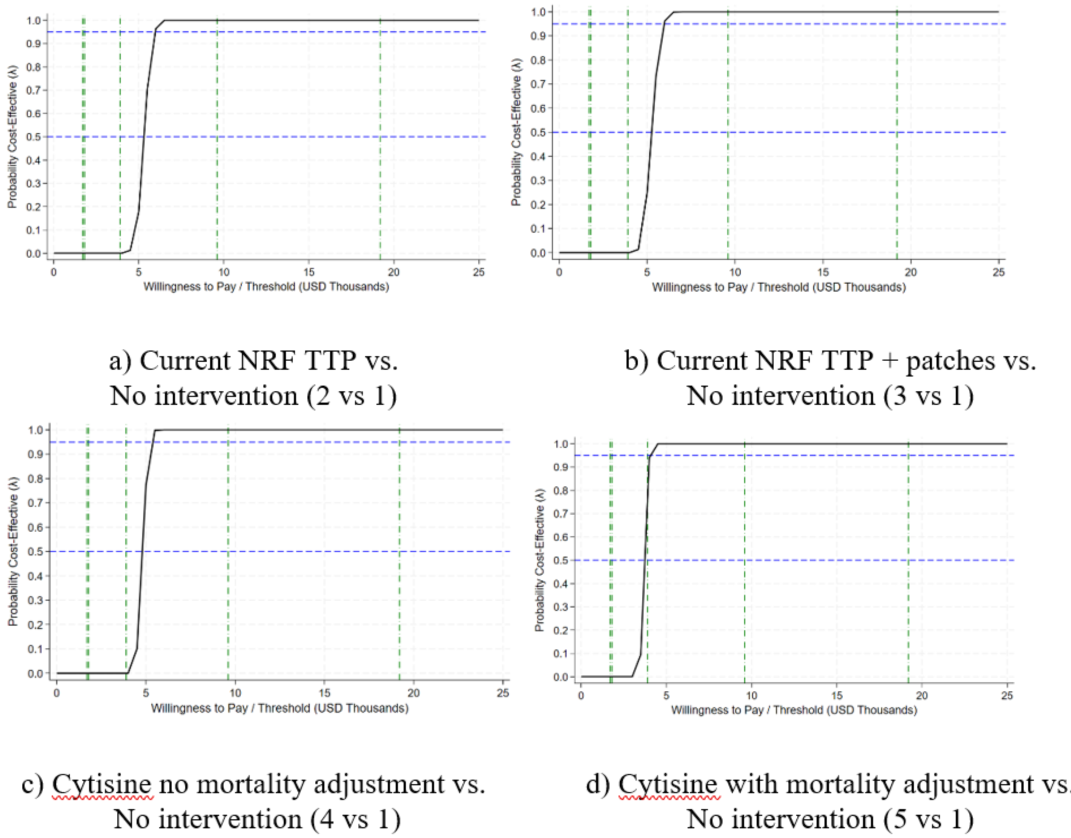


Figure 3 Cost-effectiveness acceptability curve—societal perspective.
The CEAC shows the probability that the different alternatives for tobacco cessation programmes are cost-effective (from a society perspective) compared with no intervention, using a range of values for the maximum acceptable ceiling ratio (λ). Thresholds from left to right in thousand US$: 1.7=country expenses in health per capita, 1.8=lower threshold in 2017 values from Song *et al*[40], 3.9=upper threshold in 2017 values from,[40] 9.6=0.5×GDP per capita, 2017 (World Bank), 19.2=1×GDP per capita, 2017 (World Bank). Horizontal dotted lines represent 50% and 95% probabilities. No image enhancement was performed in each subfigure. Four figures were put together based on the CEAC results for each scenario comparison. CEAC, cost-effectiveness acceptability curve; NRF, National Resources Fund; TTP, Tobacco Treatment Programme.

Although not included in our study due to the policy objectives of the NRF, the inclusion of varenicline, supported by robust evidence of long-term effectiveness, could also generate substantial health gains. In addition, population-level interventions such as quitlines and mobile-based cessation programmes (mCessation) have consistently shown high cost-effectiveness due to their low implementation costs and wide reach. These strategies may be particularly valuable complements in settings like Uruguay, where tobacco control policies are already highly developed and marginal gains from regulation alone are limited. While these interventions were not explicitly modelled here due to the lack of clearly assigned costs within the Uruguayan health system, their integration alongside pharmacological and counselling-based approaches represents a promising avenue for future policy and research.

Uruguay has already implemented the full MPOWER package, leaving limited room for additional reductions in smoking through taxation or regulation alone. As countries reach this stage, the marginal impact of new control policies diminishes, and the return to investment in cessation rises. In this environment, expanding access to evidence-based cessation support becomes the logical institutional next step for both research and policymaking.

CONCLUSION

This study evaluated the cost-effectiveness of Uruguay's TTP and alternative pharmacological strategies using real-world cessation outcomes and a Markov model informed by observed transition probabilities. All cessation interventions analysed were cost-effective compared with no intervention. Cytisine emerged as the alternative that achieves the greatest reduction in YLLs and, importantly, becomes cost-saving under both the healthcare and societal perspectives. These findings hold particular relevance in a context where the health system bears the long-term cost of treating tobacco-attributable diseases.

In summary, expanding cessation support would accelerate declines in smoking prevalence, generate gains in life expectancy and reduce future healthcare expenditure. Uruguay's longstanding leadership in tobacco control provides a strong foundation for advancing toward this next phase: moving from regulation to sustained, large-scale cessation.

Acknowledgements To Elba Esteves and Laura Llambí, for their unconditional support, which has gone far beyond the completion of this work. Their knowledge and commitment to these issues not only inspire but also spread the desire to continue exploring and learning. To the National Resources Fund (NRF) for providing the data, and its Technical Directorate for their careful reading of the first draft and the comments that allowed for improving the current version.

Contributors Idea, conceptualisation, writing: MG, IM, PT. Coding and estimation: IM. Guarantor: IM.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data is available upon request, as some of the data provided by national agencies is confidential and may not be possible to share.

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REFERENCES

1 Curry SJ, Grothaus LC, McAfee T, *et al*. Use and cost effectiveness of smoking-cessation services under four insurance plans in a health maintenance organization. *N Engl J Med* 1998;339:673–9.
2 Cadier B, Durand-Zaleski I, Thomas D, *et al*. Cost Effectiveness of Free Access to Smoking Cessation Treatment in France Considering the Economic Burden of Smoking-Related Diseases. *PLoS One* 2016;11:e0148750.
3 Cobos-Campos R, Mar J, Apiñaniz A, *et al*. Cost-effectiveness analysis of text messaging to support health advice for smoking cessation. *Cost Eff Resour Alloc* 2021;19:1–13.
4 Lee D, Lee YR, Oh IH. Cost-effectiveness of smoking cessation programs for hospitalized patients: a systematic review. *Eur J Health Econ* 2019;20:1409–24.
5 Cadham CJ, Cao P, Jayasekera J, *et al*. Cost-Effectiveness of Smoking Cessation Interventions in the Lung Cancer Screening Setting: A Simulation Study. *J Natl Cancer Inst* 2021;113:1065–73.
6 Hoogendoorn M, Feenstra TL, Hoogenveen RT, *et al*. Long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD. *Thorax* 2010;65:711–8.
7 Drouin O, Sato R, Drehmer JE, *et al*. Cost-effectiveness of a Smoking Cessation Intervention for Parents in Pediatric Primary Care. *JAMA Netw Open* 2021;4:e213927.
8 Jha P, Ramasundarahettige C, Landsman V, *et al*. 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med* 2013;368:341–50.
9 Holford TR, Meza R, Warner KE, *et al*. Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964-2012. *JAMA* 2014;311:164–71.
10 Gerstenblüth M, Triunfo P. El control del tabaco en Uruguay: evolución de los últimos 20 años. *RMU* 2024;40.
11 Instituto Nacional de Estadística (INE). Encuesta continua de hogares. 2024. Available: https://www.gub.uy/instituto-nacional-estadistica/encuesta-continua-hogares
12 Pichon-Riviere A, Alcaraz A, Palacios A, *et al*. The health and economic burden of smoking in 12 Latin American countries and the potential effect of increasing tobacco taxes: an economic modelling study. *Lancet Glob Health* 2020;8:e1282–94.
13 Esteves E, Gambogi R, Saona G, *et al*. Tratamiento de la dependencia al tabaco: experiencia del Fondo Nacional de Recursos. *Rev Urug Cardiol* 2011;26:58–64.
14 Esteves E, Saona G, Baldizzoni M, *et al*. Evaluación del programa de tabaquismo del nrf. In: *Investigación de resultados en salud. Experiencia de la Unidad de Evaluación del Fondo Nacional de Recursos*. Montevideo: Selección de trabajos, 2020.
15 Flack SA, Taylor M, Trueman P. *Cost-Effectiveness of Interventions for Smoking Cessation*. York: York Health Economics Consortium, 2007.
16 Guerriero C, Cairns J, Roberts I, *et al*. The cost-effectiveness of smoking cessation support delivered by mobile phone text messaging: Txt2stop. *Eur J Health Econ* 2013;14:789–97.
17 Husereau D, Drummond M, Augustovski F, *et al*. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *MDM Policy & Practice* 2022;7:23814683211061097.
18 Doll R, Peto R, Wheatley K, *et al*. Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ* 1994;309:901–11.
19 Doll R, Gray R, Hafner B, *et al*. Mortality in relation to smoking: 22 years' observations on female British doctors. *Br Med J* 1980;280:967–71.
20 Paulin LM, Halenar MJ, Edwards KC, *et al*. Association of tobacco product use with chronic obstructive pulmonary disease (COPD) prevalence and incidence in Waves 1 through 5 (2013-2019) of the Population Assessment of Tobacco and Health (PATH) Study. *Respir Res* 2022;23:273.
21 Junta Nacional de Drogas (JND). VII encuesta nacional sobre consumo de drogas en población general. 2019.
22 Drake I, Martich E. Tratamientos farmacológicos para la reducción de la adicción al tabaco: análisis de costo efectividad. *Rev Argent Salud Pública* 2016;7:8–13.
23 Lindson N, Theodoulou A, Ordóñez-Mena JM, *et al*. Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses. *Cochrane Database Syst Rev* 2023;9:CD015226.
24 De Santi O, Orellana M, Di Niro CA, *et al*. Evaluation of the effectiveness of cytisine for the treatment of smoking cessation: A systematic review and meta-analysis. *Addiction* 2024;119:649–63.
25 Rigotti NA, Benowitz NL, Prochaska JJ, *et al*. n.d. Cytisinicline for Smoking Cessation: The ORCA Phase 3 Replication Randomized Clinical Trial. *JAMA Intern Med*.
26 Cao P, Jeon J, Levy DT, *et al*. Potential Impact of Cessation Interventions at the Point of Lung Cancer Screening on Lung Cancer and Overall Mortality in the United States. *J Thorac Oncol* 2020;15:1160–9.
27 Sandoval GA, Totanes R, David AM, *et al*. Case for investment in tobacco cessation: a population-based analysis in low- and middle-income countries. *Rev Panam Salud Publica* 2022;46:e71.
28 Benavides MG. Terapia farmacológica de primera línea en cesación tabáquica. *Revista Médica Clínica Las Condes* 2024;35:161–8.
29 Rábade-Castedo C, Granda-Orive JI, Riesco-Miranda JA, *et al*. Guía separ de práctica clínica de tratamiento farmacológico del tabaquismo.
30 Wise J. NICE proposes adding cytisine as treatment option for smoking cessation. *BMJ* 2024;q2563.
31 Shang X, E F, Guo K, *et al*. Effectiveness and Safety of Varenicline for Smoking Cessation: An Overview and Meta-analysis. *J Addict Med* 2023;17:536–43.
32 Thomas KH, Dalili MN, López-López JA, *et al*. Comparative clinical effectiveness and safety of tobacco cessation pharmacotherapies and electronic cigarettes: a systematic review and network meta-analysis of randomized controlled trials. *Addiction* 2022;117:861–76.
33 Wu Q, Gilbody S, Peckham E, *et al*. Varenicline for smoking cessation and reduction in people with severe mental illnesses: systematic review and meta-analysis. *Addiction* 2016;111:1554–67.

34 Fagerström KO. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addict Behav* 1978;3:235–41.
35 Heatherton TF, Kozlowski LT, Frecker RC, *et al*. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict* 1991;86:1119–27.
36 Walker N, Smith B, Barnes J, *et al*. Cytisine versus varenicline for smoking cessation in New Zealand indigenous Māori: a randomized controlled trial. *Addiction* 2021;116:2847–58.
37 Herd N, Borland R, Hyland A. Predictors of smoking relapse by duration of abstinence: findings from the International Tobacco Control (ITC) Four Country Survey. *Addiction* 2009;104:2088–99.
38 Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction* 2004;99:29–38.
39 National Institute for Health and Care Excellence (NICE). Economic modelling methods for smoking cessation (ph15/ng209). London NICE; 2008. Available: https://www.nice.org.uk/guidance/ng209/evidence
40 Song F, Raftery J, Aveyard P, *et al*. Cost-effectiveness of pharmacological interventions for smoking cessation: a literature review and a decision analytic analysis. *Med Decis Making* 2002;22:S26–37.
41 World Bank. GDP per capita (current US$) – uruguay (indicator NY.GDP.PCAP.CD). World Bank; 2025. Available: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=UY
42 Iino H, Hashiguchi M, Hori S. Estimating the range of incremental cost-effectiveness thresholds for healthcare based on willingness to pay and GDP per capita: A systematic review. *PLoS One* 2022;17:e0266934.
43 Fenwick E, Marshall DA, Levy AR, *et al*. Using and interpreting cost-effectiveness acceptability curves: an example using data from a trial of management strategies for atrial fibrillation. *BMC Health Serv Res* 2006;6:52.
44 Mahalingam V, Santhanakrishnan RK, Malaisamy M, *et al*. Cost-effectiveness analysis for implementation of smoking cessation strategies at primary health care settings in Tamil Nadu. *PLoS One* 2025;20:e0318013.
45 Mar J, Antoñanzas F, Pradas R, *et al*. Los modelos de Markov probabilísticos en la evaluación económica de tecnologías sanitarias: una guía práctica. *Gac Sanit* 2010;24:209–14.
46 Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation.* Oxford: Oxford University Press, 2006.
47 Smith CE, Hill SE, Amos A. Impact of specialist and primary care stop smoking support on socio-economic inequalities in cessation in the United Kingdom: a systematic review and national equity initial review completed 22 January 2019; final version accepted 19 July 2019 analysis. *Addiction* 2020;115:34–46.
48 Córdoba García R, Guillem FC. Nuevos fármacos financiados para la deshabituación del tabaco. *Atención Primaria* 2023;55:102647.
49 Harris JE, Balsa AI, Triunfo P. Tobacco control campaign in Uruguay: Impact on smoking cessation during pregnancy and birth weight. *J Health Econ* 2015;42:186–96.
50 Brown RA, Palm Reed KM, Bloom EL, *et al*. A randomized controlled trial of distress tolerance treatment for smoking cessation. *Psychol Addict Behav* 2018;32:389–400.
51 West R, Zatonski W, Cedzynska M, *et al*. Placebo-controlled trial of cytisine for smoking cessation. *N Engl J Med* 2011;365:1193–200.
52 Bang H, Zhao H. Cost-effectiveness analysis: a proposal of new reporting standards in statistical analysis. *J Biopharm Stat* 2014;24:443–60.
53 World Health Organization. WHO guide for standardization of economic evaluations of immunization programmes. World Health Organization; 2019. Available: https://iris.who.int/server/api/core/bitstreams/9d28ecfa-ae0a-405b-ad8c-74b01267725c/content
54 National Institute for Health and Care Excellence (NICE). Health technology evaluations: the manual (PMG36). London NICE; 2025. Available: https://www.nice.org.uk/process/pmg36
55 International Decision Support Initiative (iDSI). Guide to rapid review of international hta reports. Washington (DC) Center for Global Development; 2024. Available: https://www.cgdev.org/sites/default/files/2024-iDSI-aHTA-Guide.pdf
56 Chen B, Silvestri GA, Dahne J, *et al*. The Cost-Effectiveness of Nicotine Replacement Therapy Sampling in Primary Care: a Markov Cohort Simulation Model. *J Gen Intern Med* 2022;37:3684–91.
57 Peto R, Darby S, Deo H, *et al*. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *BMJ* 2000;321:323–9.
58 Wang QL, Xie SH, Li WT, *et al*. Smoking Cessation and Risk of Esophageal Cancer by Histological Type: Systematic Review and Meta-analysis. *J Natl Cancer Inst* 2017;109.