SUPPLEMENTARY MATERIAL

Methods

Our proposed hybrid model integrates a continuous-time agent-based model (ABM) with a Markov model for vaccination uptake, incorporating the susceptible-exposed-infected-hospitalized-removed/recovered (SEIHR) framework for epidemic transmission dynamics.

The SEIHR model was implemented to simulate epidemic spread within a randomly mixed population. This model, an extension of the SEIR framework, was adapted from Yanjin Wang, Pei Wang et al. (*1*), who studied COVID-19 transmission in Wuhan following lockdown measures, when population movement was restricted and disease control measures were in place. The population was stratified into five compartments: susceptible (S), exposed (E), infected (I), hospitalized (H), and removed/recovered (R). Given the relatively short time horizon, population dynamics and disease-related mortality were considered negligible; thus, the total population size N remained constant, and a death state was not included. The infected compartment represented outpatient cases, with severe cases transitioning to the hospitalized state and others moving directly to the removed state upon recovery. The SEIHR model dynamics are described by the following system of nonlinear ordinary differential equations.

$$\begin{cases} \frac{dS(t)}{dt} = -\beta\left(1-\frac{I(t)}{N}\right)\frac{I(t)}{N}S(t) \\ \frac{dE(t)}{dt} = \beta\left(1-\frac{I(t)}{N}\right)\frac{I(t)}{N}S(t) - \lambda E(t) \\ \frac{dI(t)}{dt} = \lambda E(t) - \alpha I(t) - \gamma I(t) \\ \frac{dH(t)}{dt} = \alpha I(t) - \mu H(t) \\ \frac{dR(t)}{dt} = \gamma I(t) + \mu H(t) \end{cases}$$

Here, N represents the total population size, $N = S(t) + E(t) + I(t) + H(t) + R(t)$; denotes the progression rate from state S to E; λ represents the rate of progression to I; α indicates the daily rate of progression from infected to hospitalized state; γ represents the recovery rate from I to R; and μ denotes the daily rate of progression from H to R.

A continuous-time agent-based SEIHR model for a randomly mixed population was developed by transforming the compartmental model into an ABM framework. The mathematical equivalence between deterministic compartmental models and their corresponding stochastic ABMs has been established in the literature (*2*–*3*). Individual vaccination status was modeled through a Markov process based on ABM simulation outcomes and vaccination compliance strategies. This innovative integration of a continuous-time ABM with a Markov model enables comprehensive economic evaluation of vaccination compliance strategies for infectious diseases. The schematic representations of the SEIHR model and the hybrid model are illustrated in Figure 1A and 1B, respectively. A detailed description of our proposed hybrid model follows.

The influenza transmission dynamics were simulated through random interactions within the baseline population. An initial population of N agents was generated according to age group proportions. In the first cycle (365 days), agents were randomly selected for vaccination based on age-specific baseline coverage rates. A proportion of agents equal to N times the attack rate was randomly designated as infected (I), with the remaining agents classified as susceptible (S). Each agent was assigned five potential events, with event times determined by adding a waiting time to the current time. These events comprised:

An exposure event for susceptible agents, with waiting time drawn from an exponential distribution parameterized by the age-specific exposure rate β multiplied by the corresponding age-specific exposure vaccination multiplier ($m_{\beta v}$), if applicable (i.e., $\beta m_{\beta v}$);

An infection event for exposed agents, with waiting time drawn from an exponential distribution parameterized by the age-specific rate λ;

A hospitalization event for infected agents, with waiting time drawn from an exponential distribution parameterized by the age-specific infection rate α multiplied by the corresponding age-specific hospitalization

vaccination multiplier ($m_{\alpha v}$), if applicable (i.e., $\alpha m_{\alpha v}$);

A hospitalization progression event for infected agents, with waiting time drawn from an exponential distribution parameterized by the age-specific rate μ;

A recovery event for hospitalized agents, with waiting time drawn from an exponential distribution parameterized by the age-specific rate γ.

The vaccination multipliers were implemented to modify the exposure rate (β) and hospitalization rate (α) for agents across different age groups based on vaccination status. Vaccinated agents' exposure rates were adjusted by the exposure vaccination multiplier ($m_{\beta v}$), resulting in an effective exposure rate of $\beta m_{\beta v}$. Similarly, their hospitalization rates were modified by the hospitalization vaccination multiplier ($m_{\alpha v}$), yielding an effective rate of $\alpha m_{\alpha v}$. Unvaccinated agents retained their baseline rates (β and α, respectively). These multipliers quantified the protective effects of vaccination by reducing the probability of exposure and hospitalization among vaccinated individuals.

The simulation progressed sequentially through event times, with states updated according to the following algorithm.

For exposed/transmission events, a contact was randomly selected assuming uniform population distribution. If the selected contact was in a susceptible state, they transitioned to an exposed state, and an infection event was subsequently scheduled for the exposed agent.

For infection events, the agent transitioned to the infected state, with both recovery and hospitalization events scheduled for the infected individual.

For hospitalization events, the agent transitioned to the hospitalized state, with a recovery event scheduled for their hospitalized status.

For recovery events, the agent was classified as removed, and all remaining scheduled events for that agent were cleared. The removed agent gained immunity and became non-susceptible to infection for the duration of the current cycle.

Events were processed chronologically, with the earliest event executed first, followed by evaluation of subsequent events. This sequence continued until either all events were processed or the simulation reached its designated endpoint of one year (365 days).

Following the ABM simulation cycle, population-wide vaccination for the subsequent cycle was implemented using a Markov model. Each agent's vaccination probability for the next cycle was determined by the vaccination compliance policy, based on both their infection status at the conclusion of the ABM simulation and their vaccination status at the start of the current cycle. The ABM simulation process was then repeated. Each complete cycle consisted of a Markov model-based vaccination process followed by an ABM disease propagation simulation, with multiple cycles executed according to the specified duration. This framework constituted our continuous-time hybrid model combining ABM and Markov approaches for evaluating vaccination compliance strategies in infectious disease contexts.

Hybrid Model Simulation

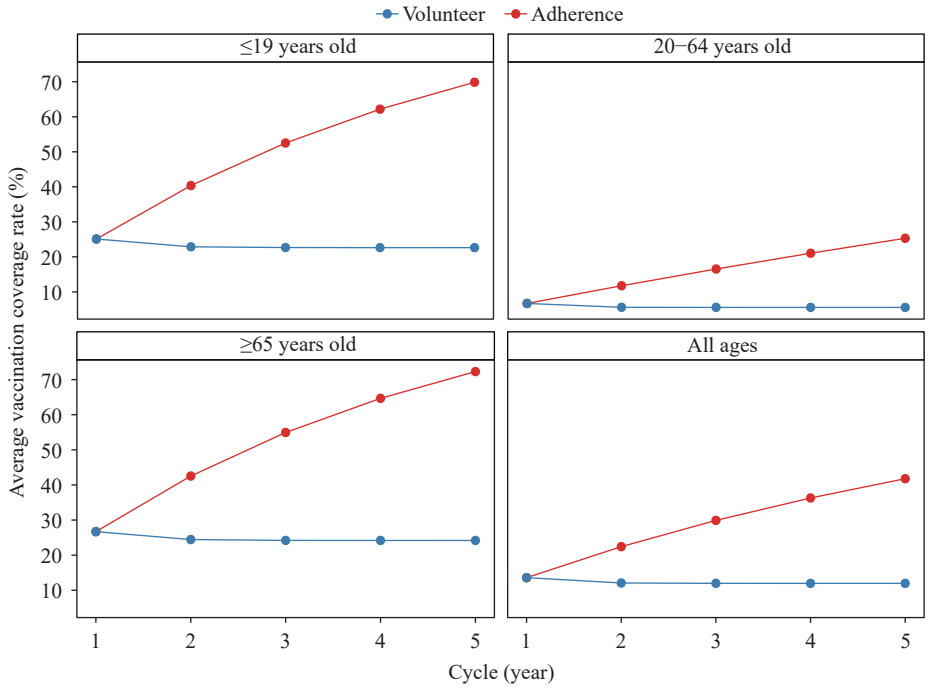
The analysis of vaccination coverage across five annual cycles (Supplementary Table S1 and Supplementary Figure S1) reveals distinct patterns between the "volunteer" and "adherence" strategies.

SUPPLEMENTARY TABLE S1. Additional parameter settings for PSA.

Parameters	Age groups					
	Age group 1 (≤19 years old)		Age group 2 (20–64)		Age group 3 (≥65)	
	Value	Distribution	Value	Distribution	Value	Distribution
Attack rate	(0.008, 0.012)	Uniform	(0.008, 0.012)	Uniform	(0.008, 0.012)	Uniform
Baseline vaccination coverage	(0.226, 0.276)	Uniform	(0.064, 0.070)	Uniform	(0.238, 0.297)	Uniform
QALY multiplier	(0.95, 1.05)	Uniform	(0.95, 1.05)	Uniform	(0.95, 1.05)	Uniform
Cost per day multiplier	I: (448.51, 0.35) H: (178.55, 4.67)	Gamma	I: (448.51, 0.35, 0) H: (178.55, 4.67, 234.79)	Noncentral Gamma	I: (448.51, 0.35) H: (178.55, 4.67)	Gamma

Note: Uniform (a,b) represents the uniform distribution with minimum a and maximum b. Gamma (a,b) represents the gamma distribution with shape parameter a and scale parameter b. Noncentral gamma (a,b,c) represents the noncentral gamma distribution with shape parameter a, scale parameter b, and noncentrality parameter c.

Abbreviation: PSA=probabilistic sensitivity analysis; QALY=quality-adjusted life year.



SUPPLEMENTARY FIGURE S1. Average vaccination coverage over five annual cycles of the hybrid model simulation results for the influenza vaccination compliance strategies.

Under the "volunteer" strategy, vaccination decisions are made annually based on individuals' influenza infection experience in the previous year. The general population's average coverage showed a modest decline, starting at 13.6% in Cycle 1 and decreasing to 12.0% by Cycle 5. Coverage among those ≤19 years old decreased from 25.1% to 22.6%, potentially reflecting lower perceived influenza risk in this age group. The 20-64 years age group maintained the lowest coverage, declining from 6.7% to 5.6%. The ≥65 years group sustained the highest coverage, though decreasing from 26.7% to 24.2%.

The "volunteer" strategy demonstrated a characteristic pattern of initial decline followed by stabilization. After the general population's coverage dropped from 13.6% to 12.0% between Cycles 1 and 2, it maintained this level through Cycle 5. Similarly, the ≤19 years group stabilized at 22.9% after an initial decrease from 25.1%, while the 20–64 years group leveled at 5.6% following a decline from 6.7%. The ≥65 years group's coverage stabilized at 24.4% after decreasing from its initial 26.7%.

Under the "adherence" strategy, individuals who have previously received vaccination maintain their vaccination status in subsequent years, while those who have not been vaccinated follow decision-making patterns similar to the "volunteer" strategy, basing their annual vaccination decisions on their previous year's influenza experience. This approach yields substantially higher and progressively increasing coverage rates. The general population's average coverage initiated at 13.6% in Cycle 1 (matching the "volunteer" strategy's baseline) but demonstrated significant growth, reaching 41.8% by Cycle 5. The youngest age group exhibited remarkable improvement from 25.1% to 69.9%, illustrating the cumulative effect of sustained vaccination behavior. The 20–64 years group, despite starting at a lower 6.7%, achieved a substantial increase to 25.3%. The oldest group demonstrated the most pronounced improvement, with coverage expanding from 26.7% in Cycle 1 to 72.3% in Cycle 5.

The marked increase in coverage under the "adherence" strategy can be attributed to its built-in continuity mechanism, which maintains individuals' vaccination status once initiated. This contrasts sharply with the "volunteer" strategy, where despite annual decision opportunities, coverage shows an initial decline followed by stabilization, as vaccination decisions remain solely dependent on the previous year's influenza experience.

Figure 2 presents a comprehensive cost-effectiveness evaluation of both strategies across all cycles through four key analytical visualizations.

The comprehensive analysis of vaccination coverage and cost-effectiveness metrics demonstrates clear advantages of the "adherence" strategy over the "volunteer" approach. The "adherence" strategy's superior effectiveness and

cost-effectiveness, particularly at higher WTP thresholds, stem from its sustained vaccination patterns. The resulting improvements in health outcomes, measured in QALYs, provide robust justification for the strategy's increased implementation costs across multiple WTP thresholds.

Probabilistic Sensitivity Analysis

We conducted probabilistic sensitivity analysis by establishing probability distributions for key parameters including attack rate, baseline vaccination coverage, QALY multiplier, and cost per day multiplier. The complete parameter specifications are detailed in Supplementary Table S2. The comprehensive results are presented in Supplementary Tables S3–S4, Supplementary Figures S2–S3.

The PSA results corroborated our primary hybrid model simulation findings. The incremental cost-effectiveness ratio was 34,432 Chinese Yuan (CNY), marginally higher than the CNY33,847 calculated in the primary analysis (Supplementary Table S3). Vaccination coverage patterns across the five annual cycles closely mirrored those observed in the primary analysis (Supplementary Table S3 and Supplementary Figure S2). In the cost-effectiveness plane (Supplementary Figure S3A), the WTP threshold of CNY85,698 is represented by a dashed line, with points below this line indicating cost-effective outcomes. The analysis revealed that 74.1% of simulated points were cost-effective, with 29.4% demonstrating dominance through both cost savings and health improvements. The cost-effectiveness acceptability curve (Supplementary Figure S3B) and cost-effectiveness acceptability frontier (Supplementary Figure S3C) demonstrated that the "adherence" strategy's probability of cost-effectiveness increases substantially when the WTP exceeds the ICER of CNY34,432, indicating its superiority over the "volunteer" strategy. However, the convergence to complete cost-effectiveness probability was more gradual compared to the

SUPPLEMENTARY TABLE S2. Average vaccination coverage over five annual cycles of the hybrid model simulation results for the influenza vaccination compliance strategies.

Age group (years old)	Cycle (year)	Average vaccination coverage rate (%) (95% *CI*)	
		"Adherence" strategy	"Volunteer" strategy
All ages	1	13.594 (13.592, 13.596)	13.594 (13.592, 13.596)
	2	12.078 (12.076, 12.080)	22.426 (22.423, 22.428)
	3	11.978 (11.976, 11.980)	29.904 (29.901, 29.907)
	4	11.970 (11.968, 11.972)	36.289 (36.286, 36.292)
	5	11.971 (11.969, 11.973)	41.785 (41.782, 41.788)
Age group 1 (≤19)	1	25.100 (25.095, 25.106)	25.100 (25.095, 25.106)
	2	22.874 (22.869, 22.880)	40.370 (40.363, 40.376)
	3	22.661 (22.656, 22.667)	52.512 (52.505, 52.518)
	4	22.635 (22.630, 22.641)	62.174 (62.167, 62.180)
	5	22.639 (22.633, 22.645)	69.866 (69.859, 69.872)
Age group 2 (20–64)	1	6.701 (6.699, 6.703)	6.701 (6.699, 6.703)
	2	5.592 (5.591, 5.594)	11.752 (11.749, 11.754)
	3	5.563 (5.562, 5.565)	16.527 (16.524, 16.530)
	4	5.564 (5.562, 5.565)	21.040 (21.036, 21.043)
	5	5.564 (5.562, 5.566)	25.307 (25.303, 25.310)
Age group 3 (≥65)	1	26.702 (26.695, 26.710)	26.702 (26.695, 26.710)
	2	24.451 (24.444, 24.458)	42.541 (42.533, 42.549)
	3	24.207 (24.200, 24.214)	54.945 (54.937, 54.953)
	4	24.192 (24.185, 24.199)	64.670 (64.662, 64.678)
	5	24.191 (24.184, 24.198)	72.294 (72.287, 72.301)

Note: The outcome values are estimated average vaccination coverage percentages. 95% of *CI*s are obtained by the Clopper and Pearson method (*4*).
Abbreviation: *CI*=confidence interval.

SUPPLEMENTARY TABLE S3. Summary of the hybrid model PSA results for the influenza vaccination compliance strategies.

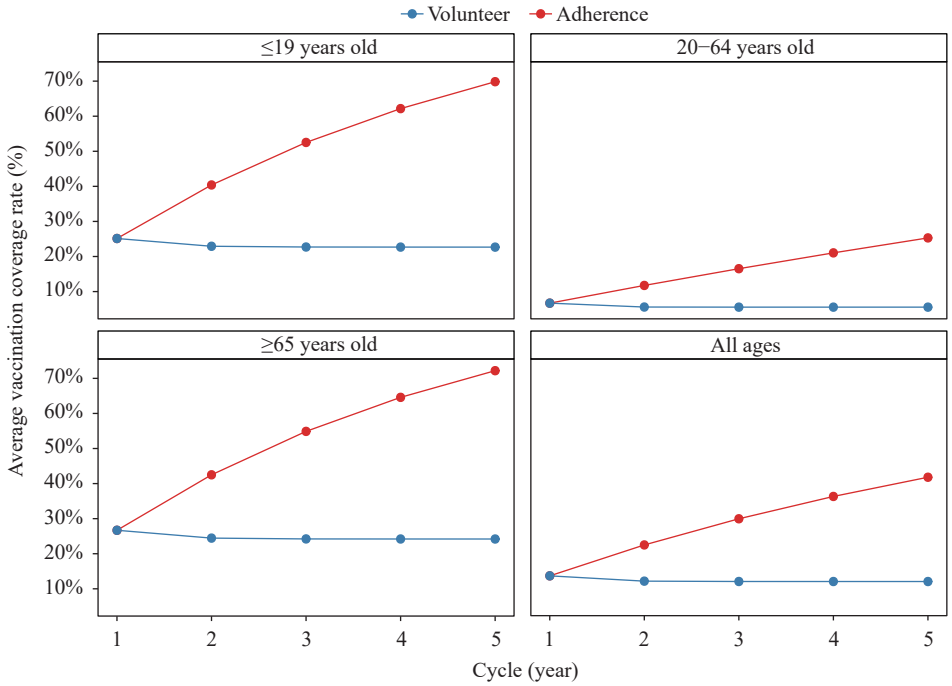
Outcome	"Adherence" *vs.* "Volunteer" [Estimate (95% *CI*)]
Incremental vaccination number	823.154 (822.438, 823.870)
Decremental infection number	22.506 (22.344, 22.667)
Decremental inpatient number	19.577 (19.436, 19.719)
Decremental outpatient number	2.928 (2.906, 2.951)
Incremental vaccination ratio (%)	133.658 (133.470, 133.846)
Decremental infection ratio (%)	16.252 (16.206, 16.298)
Decremental inpatient ratio (%)	15.833 (15.785, 15.880)
Decremental outpatient ratio (%)	19.746 (19.681, 19.811)
WTP threshold (CNY)	85,698
Incremental QALYs	0.091 (0.066, 0.122)
Incremental costs (CNY)	3,118 (−8,124, 13,409)
Incremental NMB (CNY)	4,642 (−6,878, 16,965)
ICER (CNY per QALY)	34,432

The outcome values are for every 1,000 individuals for 5 years.
Abbreviation: *CI*=confidence interval; CNY=Chinese Yuan; ICER=incremental cost-effectiveness ratio; NMB=net monetary benefit; PSA=probabilistic sensitivity analysis; QALY=quality-adjusted life year; WTP=willingness to pay.

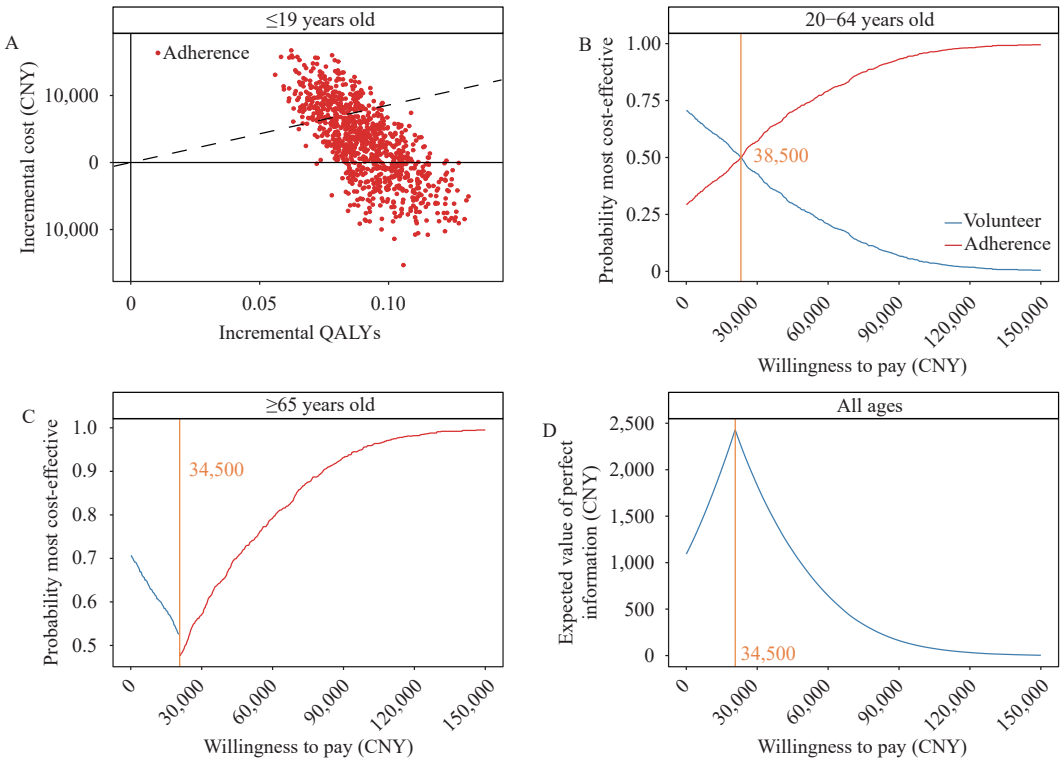
SUPPLEMENTARY TABLE S4. Average vaccination coverage over five annual cycles of the hybrid model PSA results for the influenza vaccination compliance strategies.

Age group (years old)	Cycle (year)	Average vaccination coverage rate (%) (95% *CI*)	
		"Adherence" strategy	"Volunteer" strategy
All ages	1	13.598 (13.596, 13.600)	13.598 (13.596, 13.600)
	2	12.087 (12.085, 12.089)	22.424 (22.421, 22.426)
	3	11.988 (11.986, 11.990)	29.895 (29.892, 29.898)
	4	11.981 (11.979, 11.983)	36.271 (36.268, 36.274)
	5	11.978 (11.976, 11.980)	41.759 (41.756, 41.762)
Age group 1 (≤19 years old)	1	25.131 (25.126, 25.137)	25.131 (25.126, 25.137)
	2	22.917 (22.911, 22.923)	40.395 (40.388, 40.401)
	3	22.705 (22.700, 22.711)	52.522 (52.516, 52.529)
	4	22.683 (22.677, 22.689)	62.165 (62.158, 62.171)
	5	22.674 (22.669, 22.680)	69.839 (69.833, 69.845)
Age group 2 (20–64)	1	6.699 (6.697, 6.701)	6.699 (6.697, 6.701)
	2	5.592 (5.590, 5.594)	11.749 (11.747, 11.752)
	3	5.562 (5.560, 5.564)	16.523 (16.520, 16.526)
	4	5.562 (5.560, 5.564)	21.035 (21.031, 21.038)
	5	5.563 (5.561, 5.565)	25.300 (25.297, 25.304)
Age group 3 (≥65)	1	26.690 (26.683, 26.697)	26.690 (26.683, 26.697)
	2	24.455 (24.448, 24.462)	42.501 (42.493, 42.508)
	3	24.220 (24.213, 24.227)	54.884 (54.876, 54.892)
	4	24.202 (24.195, 24.209)	64.587 (64.579, 64.595)
	5	24.197 (24.190, 24.204)	72.190 (72.183, 72.197)

Note: The outcome values are estimated average vaccination coverage percentages. 95% of *CI*s are obtained by the Clopper and Pearson method (*4*).
Abbreviation: *CI*=confidence interval; PSA=probabilistic sensitivity analysis.



SUPPLEMENTARY FIGURE S2. Average vaccination coverage over five annual cycles of the hybrid model PSA results for the influenza vaccination compliance strategies.
Abbreviation: PSA=probabilistic sensitivity analysis.



SUPPLEMENTARY FIGURE S3. Cost-effectiveness analysis results for the PSA of the hybrid model simulations. (A) The cost-effectiveness plane. The dashed line represents the WTP threshold (85,698 CNY). (B) The cost-effectiveness acceptability curves. (C) The cost-effectiveness acceptability frontier. (D) The expected value of perfect information.
Note: The costs and QALYs are reported for every 1,000 individuals for 5 years. The population size is *N*=1,000,000 with 1,000 simulation replicates.
Abbreviation: CNY=Chinese Yuan; PSA=probabilistic sensitivity analysis; QALY=quality-adjusted life year; WTP=willingness to pay.

primary analysis. Similarly, the expected value of perfect information peaked near the ICER threshold (Supplementary Figure S3D), quantifying the potential value of uncertainty reduction through additional research. While following the same pattern as the primary analysis, the EVPI's convergence to zero occurred more gradually.

R Code

The simulation's demonstrative R code is available online as a separate file (demo.R) at https://gitee.com/jimmy838/continuous-time-agent-based-markov-hybrid-model/blob/master/demo.R.

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