Using Discretely Integrated Condition Event Simulation To Construct Quantitative Benefit–Risk Models: The Example of Rotavirus Vaccination in France

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ABSTRACT

Purpose: Although quantitative benefit–risk models (qBRms) are indisputably valuable tools for gaining comprehensive assessments of health care interventions, they are not systematically used, probably because they lack an integrated framework that provides methodologic structure and harmonization. An alternative that allows all stakeholders to design operational models starting from a standardized framework was recently developed: the discretely integrated condition event (DICE) simulation. The aim of the present work was to assess the feasibility of implementing a qBRm in DICE, using the example of rotavirus vaccination.

Methods: A model of rotavirus vaccination was designed using DICE and implemented in spreadsheet software with 3 worksheets: Conditions, Events, and Outputs. *Conditions* held the information in the model; this information changed at *Events*, and *Outputs* were special Conditions that stored the results collected during the analysis. A hypothetical French birth cohort was simulated for the assessment of rotavirus vaccination over time. The benefits were estimated for up to 5 years, and the risks in the 7 days following rotavirus vaccination versus no vaccination were assessed, with the results expressed as benefit–risk ratios.

Findings: This qBRm model required 8 Events, 38 Conditions, and 9 Outputs. Two Events cyclically updated the rates of rotavirus gastroenteritis (RVGE) and intussusception (IS) according to age. Vaccination occurred at 2 additional Events, according to the vaccination scheme applied in France, and affected the occurrence of the other Events. Outputs were the numbers of hospitalizations related to RVGE and to IS, and related deaths. The entire model was specified in a small set of tables contained in a 445-KB electronic workbook. Analyses showed that for each IS-related hospitalization or death caused, 1613 (95% credible interval, 1001–2800) RVGE-related hospitalizations and 787 (95% credible interval, 246–2691) RVGE-related deaths would be prevented by vaccination. These results are consistent with those from a published French study using similar inputs but a very different modeling approach.

Implications: A limitation of the DICE approach was the extended run time needed for completing the sensitivity analyses when implemented in the electronic worksheets. DICE provided a user-friendly integrated framework for developing qBRms and should be considered in the development of structured approaches to facilitate benefit–risk assessment. (*Clin Ther*. 2020;42:1983–1991) © 2020 GlaxoSmithKline Biologicals SA. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

INTRODUCTION

The benefits of any health care intervention have to be balanced with its risks.[1–3] To this end, conducting a comprehensive benefit–risk assessment (BRA) is essential and is the core of health care intervention conceptions and regulatory review processes.[4] Although qualitative judgments have been used in BRAs of health interventions, quantitative benefit–risk models (qBRms) may provide better consistency, transparency, and predictability of decision making.[5–7] These qBRms integrate evidence from multiple sources to quantify and put into perspective the benefits and risks of a health intervention.[4,6,8] Several modeling approaches, such as decision trees,[9,10] cohort models (also called Markov models),[11–14] discrete-event simulations,[15,16] and dynamic transmission models,[17,18] have been used, each presenting its own strengths and weaknesses.[4,8] Despite efforts to promote their use, qBRms are not systematically used for BRAs, probably owing to their perceived complexity and the absence of an integrated framework providing methodologic structure and harmonization.[8,19–21] The latter is crucial for ensuring transparency, with the aim of supporting informed decision making.[4,8]

Recently, an alternative for designing and structuring decision-analytic models was developed: the *discretely integrated condition event* (DICE) simulation.[22] DICE brings together the common modeling approaches into a standardized framework that can be used by any stakeholder to structure a decision problem. A DICE model is conveniently specified in a series of tables that follow a consistent format, and the simulation can be fully implemented in spreadsheet software, making design, analysis, review, and validation straightforward.[23]

Although DICE simulation is increasingly applied in health economics,[24–28] it has not yet been used for BRA. It was tempting to challenge this novel approach with actual problems of BRA. The aim of the work was to test the use of DICE to implement a qBRm and examine its advantages and limitations.

This was done using the example of rotavirus vaccination.

MATERIALS AND METHODS
DICE Approach

In DICE, a model is specified in terms of conditions, events, and outputs. *Conditions* represent all information in the model, such as demographics, treatment characteristics, processes, the environment, the timing of events, model controls, random number, run settings and other inputs. They are tabulated using spreadsheet software (Excel 2016; Microsoft Corporation, Redmond, Washington). *Events* are points in time at which the values of some conditions change. These changes in event times, accumulating outputs, or other conditions are formulated as text expressions that respect Excel syntax but do not have the leading equals sign. These event consequences are also tabulated in an Events worksheet. *Outputs* are special conditions that store results and are tabulated on a corresponding worksheet. The events are executed by a simple open-source macro (Visual Basic for Applications; Microsoft) that loops through each Events table, row by row, sequentially inserting an equals sign in front of each text expression to convert it into an active Excel formula.[22,29]

Rotavirus Vaccination in France

Rotavirus gastroenteritis (RVGE) in young children can lead to hospitalization and even death.[30–32] Rotavirus vaccines have led to significant declines in RVGE-related morbidity and mortality.[33–36] Although rotavirus vaccines have proved to be effective, a small increased risk for intussusception (IS)—a rare, but potentially serious, condition in which a segment of the intestine invaginates into an adjacent segment[37–39])—has been observed, typically within 7 days of vaccination.[39–42]

Two live, attenuated oral rotavirus vaccines, Rotarix®[1] and RotaTeq®,[2] are licensed for use in France, with neither recommended over the other. In 2015, after a report of 2 IS-related fatalities in

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French infants following vaccination, the Haut Conseil de la Santé Publique suspended the previous recommendation on rotavirus vaccination from the French Technical Committee for Pharmacovigilance.[43,44] In such a situation, when new safety data become available, it is important to put them into the perspective of the benefit—risk profile of the intervention. To this end, qBRms can be particularly helpful as they allow for the comparison of quantitative estimates of the benefits (eg, vaccine-preventable RVGE—related hospitalizations and deaths) with the risks (eg, vaccine-induced IS—related hospitalizations and deaths) and allow for extensive sensitivity and scenario analyses. A qBRm of the Rotarix® vaccine in France was designed and implemented using DICE.

Case Study

The case study to test the utility of DICE in the implementation of a qBRm using the Rotarix® vaccine was conducted by using inputs available from the literature. The Rotarix® vaccination course consists of 2 oral doses, with the first given at 6 weeks of age, the 2 doses separated by at least 4 weeks, and the vaccination course being completed before age 24 weeks.[45] The benefits considered were the numbers of vaccine-preventable RVGE-related hospitalizations and deaths, and the risks considered were the numbers of vaccine-induced IS—related hospitalizations and deaths. A theoretic cohort aged from birth to 5 years was modeled because this range defines the period of immunization benefits,[30−32,45] most commonly used for measuring RVGE burden. Furthermore, infants are vaccinated during their first year, and vaccine-induced IS occurs shortly after vaccination.[39,40,42]

RESULTS

The DICE qBRm stores the required information on 38 conditions (see Supplemental Table S1 in the online version at https://doi.org/10.1016/j.clinthera.2020.08.013) covering the course without vaccination (hospitalization and case-fatality rates related to RVGE, and to IS) and with the vaccination (age at vaccination, compliance with second dose, effectiveness against RVGE, and relative risk for IS after doses 1 and 2). Other conditions helped to structure the model, such as simulation time, the time horizon signaling the end of the simulation, duration

of cycles (time to the next occurrence of cyclical events), and intervention strategy (no vaccination versus vaccination).

Eight events (see Supplemental Table S2 in the online version at https://doi.org/10.1016/j.clinthera.2020.08.013) handled disease occurrences (RVGE and IS), vaccine administration (dose 1: Vaccinate1; dose 2: Vaccinate2), onset of vaccine effectiveness 2 weeks after vaccination (VaccineEff), increased risk for IS at 7 days postvaccination (ISinduced), and the mandatory modeling events (Start and End).

Nine outputs specified hospitalizations and deaths related to RVGE and to IS for each strategy, as well as the number of replications to run (see Supplemental Table S3 in the online version at https://doi.org/10.1016/j.clinthera.2020.08.013).

The general DICE macro (https://www.evidera.com/dice) triggered Start first, in which: (1) the intervention strategy was assigned (no vaccination vs vaccination) and (2) time to Vaccinate1 was derived (if vaccination strategy). Then, RVGE event rates were applied every month, and IS rates, every week. During each RVGE and IS event: (1) the number of hospitalizations was estimated by applying the age-specific hospitalization rate obtained using parametric functions[46]; (2) the number of deaths was computed by applying the case-fatality rate to the hospitalizations; and (3) deaths were subtracted from the cohort. During each Vaccinate event: (1) coverage was updated and (2) ISinduced and VaccineEff events were scheduled. ISinduced occurs daily for 7 days after vaccination, with these consequences: (1) relative risk for IS was updated; (2) number of IS hospitalizations induced by vaccination was computed by applying the relative risk to the age-specific IS hospitalization rate in the proportion of the cohort covered; (3) number of IS deaths induced by vaccination was calculated by applying the IS case-fatality rate; and (4) deaths were subtracted from the cohort. At VaccineEff, which occurs 2 weeks after vaccination: (1) effectiveness was updated; and (2) this affected the numbers of hospitalizations and deaths in the following RVGE events by decreasing the age-specific RVGE-related hospitalization rate. At every event, age was updated, and the next event was triggered based on its scheduled time. At the end of the time horizon (5 years), the End event was executed. The final accrual of outputs is reported in the Figure 1.
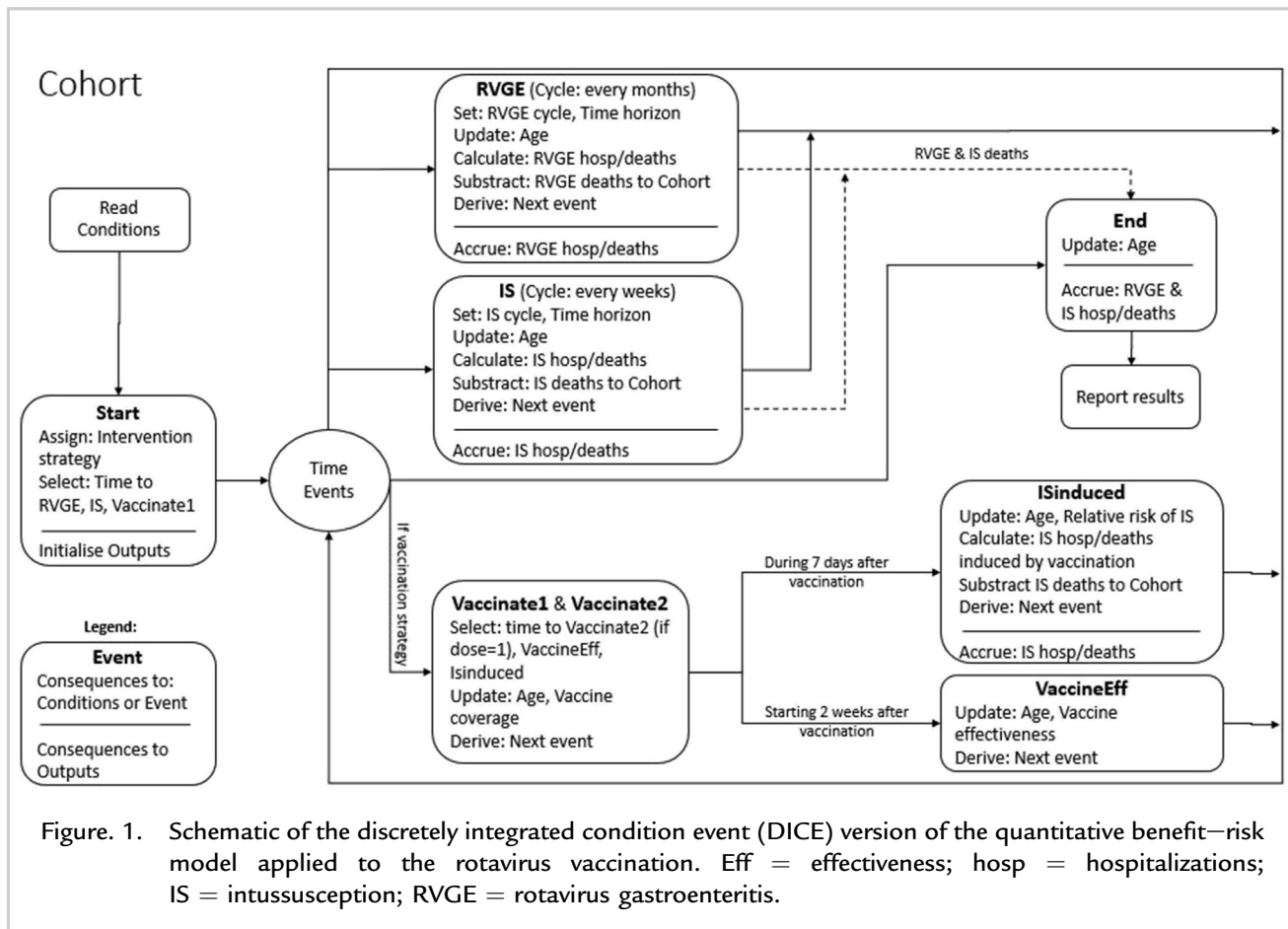
Figure. 1. Schematic of the discretely integrated condition event (DICE) version of the quantitative benefit—risk model applied to the rotavirus vaccination. Eff = effectiveness; hosp = hospitalizations; IS = intussusception; RVGE = rotavirus gastroenteritis.

The differences between the 2 strategies, in numbers of hospitalizations and deaths related to RVGE and to IS, were used for determining the hospitalization and death benefit—risk ratios (BRRs). Appropriate distributions were fitted to inputs with parameter uncertainty (Table I). These distributions were used for random sampling in probabilistic sensitivity analyses, with up to 10^4 replications, to evaluate how uncertainty in these parameters would affect outcomes.

The entire model was specified in a small set of tables contained in a 445-KB Excel workbook. In the absence of a rotavirus vaccination program, the French birth cohort (mean births, 791,183 per annum during 2006—2014) would be expected to experience a mean (95% credible interval) of 15,010 (12,058—18,390) RVGE-related hospitalizations and 10.13 (4.57—19.38) RVGE-related deaths over 5 years, as well as 326 (258—401) IS-related hospitalizations and 0.45 (0.18—0.97) IS-related deaths in infants aged <1 year (Table II). Vaccination would be expected to prevent 12,553 (9949—15,580) RVGE-related hospitalizations and 8.47 (3.81—16.22) deaths, but to cause 7.76 (4.70—11.86) IS-related hospitalizations and 0.0107 (0.0038—0.0251) IS-related deaths. A BRR for hospitalizations of 1613 (1001—2800) was estimated, meaning that for each IS-related hospitalization caused, 1613 RVGE-related hospitalizations would be prevented by vaccination; with regard to deaths, the BRR was 787 (246—2691). The DICE results confirm that the 2-dose schedule of rotavirus vaccination would prevent a substantial number of RVGE cases at the cost of a small increase in the number of IS cases. These findings are consistent with those published in a 2018 study that used similar inputs but in a quite different model framework,[46] with absolute differences of <1% in rates without vaccination, and of ~10% in RVGE cases prevented and IS induced following vaccination. The BRR

Table I. Inputs subject to parameter uncertainty used in probabilistic sensitivity analysis in the DICE qBRm.

Input	Median (95% CrI)[*]	Distribution[†]
Demography		
Age at 1st dose, wk	9.47 (6.17−22.21)	γ (2861; 0.000871)
Delay before 2nd dose, wk	4.78 (3.38−10.87)	γ (2239; 0.000566)
Age at 2nd dose, wk	14.73 (11.03−28.16)	Derived from 2 distributions above
Compliance with 2nd dose	0.92 (0.72−0.99)	β (14.43, 1.60)
Benefit		
Baseline hospitalization rate related to RVGE/10^5 children/y		
<3 y	604.0 (526.9−688.4)	γ (216; 35,711)
<5 y	380.7 (305.9−467.1)	γ (86; 22,534)
Mortality rate related to RVGE/10^6 children/y		
<3 y	4.08 (1.94−7.42)	γ (9; 2,125,000)
<5 y	2.56 (1.17−4.92)	Derived from 3 distributions above
RVGE fatality rate/10^5 hospitalizations	67.5 (31.7−125.0)	Derived from 2 distributions above
Vaccine effectiveness against RVGE D2	90% (81−95)	1-log-normal (Ln[0.10]; 0.341)
Ratio of vaccine effectiveness against RVGE after a 1-dose vs 2-dose schedule	0.85 (0.62−0.97)	β (13.6, 2.73)
Vaccine effectiveness against RVGE D1	75% (55−88)	Product of the 2 distributions above
Risk		
Baseline hospitalization rate related to IS/10^5 infants (aged <1 y)/y	40.85 (32.52−50.50)	γ (80;195,005)
Mortality rate related to IS/10^6 infants (aged <1 y)/y	0.597 (0.24−1.11)	γ (7;11,731,635)
IS fatality risk/10^5 IS hospitalizations	139.17 (57.32−283.30)	Derived from 2 distributions above
Relative risk for IS		
D1	5.39 (3.94−7.38)	Log-normal
SD: 0.16	SD: 0.16	
D2	1.81 (1.32−2.48)	Log-normal
SD: 0.16	SD: 0.16	

CrI = credible interval; D1 = post dose 1; D2 = post dose 2; DICE, discretely integrated condition event; IS = intussusception; RVGE, rotavirus gastroenteritis.
Data from Ledent et al.[44]
[*] The limits of 95% CrIs were determined using the 2.5%−97.5% range.
[†] Distribution parameters are β (α; β), γ (shape; rate), and log-normal (mean; SD).

Table II. Results of the simulation comparing the Ledent et al[44] with DICE model.

Outcome	Ledent et al[44] Median (95% CrI)	DICE Median (95% CrI)	Difference, %
RVGE <5 y			
Hospitalizations			
Baseline	15,059 (12,100−18,476)	15,010 (12,058−18,390)	0.33
Prevented	11,132 (7842−14,408)	12,553 (9949−15,580)	−11.31
Deaths			
Baseline	10.13 (4.64−19.46)	10.13 (4.57−19.38)	0.05
Prevented	7.43 (3.27−14.68)	8.47 (3.81−16.22)	−12.23
IS < 1 y			
Hospitalizations			
Baseline	323 (257−400)	326 (258−401)	−0.76
Excess	6.86 (2.25−38.37)	7.76 (4.70−11.86)	−11.58
Deaths			
Baseline	0.45 (0.19−0.88)	0.45 (0.18−0.97)	0.41
Excess	0.0099 (0.0024−0.060)	0.0107 (0.0038−0.0251)	−6.92
BRR			
Hospitalization	1624 (240−5243)	1613 (1001−2800)	0.72
Death	743 (93−3723)	787 (246−2691)	−5.50

BRR = benefit−risk ratio; CrI = credible interval; DICE = discretely integrated condition event; IS = intussusception; RVGE = rotavirus gastroenteritis.

estimates for hospitalizations are similar (<1% difference), and for deaths, slightly higher (by ~5%).

DISCUSSION

Several health authorities are currently considering the adoption of structured BRAs for facilitating regulatory decisions.[47,48] Despite efforts to promote their use, qBRms are not systematically used, probably owing to their perceived complexity and the absence of an integrated framework that provides methodologic structure and harmonization.[8,19−21] In the present article, we examined the feasibility of implementing a qBRm by using a simpler, standardized modeling framework: DICE. The qBRm was easily implemented in Excel using DICE, requiring no special programming and specifying the entire model in a few simple tables. The consistency of the results with those from previous analyses carried out by programming in SAS software[46] is reassuring.

Decision makers have shown a marked preference for models implemented in spreadsheets because reviewing them does not require programming skills.[49] A DICE model is fully implemented in spreadsheets using a standard framework and terminology. The structuring choices that define the model are straightforward and, thus, easy to communicate and to understand by physicians, modelers, reviewers, decision makers, and other stakeholders.[22]

Another advantage of implementing a model in DICE is that it can accommodate any aspect in a single template, from basic models to vast, complex structures.[28] The framework could be easily modified, without necessitating additional specific programming skills. These changes could notably include: (1) transposing the cohort model to a patient-level model in order to address the heterogeneity in the determinants of the course (eg, age, sex, genetic makeup)[50] or RVGE[51,52] and IS[37,38,53] risk factors; (2) estimating the impact of vaccination on outpatient visits[14]; (3) taking into account the herd immunity effects of rotavirus vaccination[54]; and/or (4) updating the cohort by considering deaths attributable to causes other than RVGE and IS

during the time periods considered in the simulation. Therefore, the availability of DICE may encourage a broader group of modelers to use more sophisticated, realistic approaches.

A limitation of DICE, when implemented in Excel, is the extended run time required to complete the probabilistic sensitivity analysis: ~8 h for 10,000 simulations. In the basic DICE version, the repeated interactions between the macro code and the spreadsheets, slow down execution. Minimizing the number of times the macro interacts with the worksheets cuts run time substantially. However, this limitation is currently obsolete since a faster version that uses a compiled macro for reducing run time by > 300-fold is now available.[28] Another limitation of using Excel for these simulations was that some statistical functions, such as the Dirichlet-multinomial distribution, were not available. However, these distributions can be implemented as user-defined functions.

CONCLUSIONS

This study implemented a qBRm using DICE methodology. DICE simulation allows for designing and implementing a decision-analytic model without the need for customized programming. Indeed, the formulation is user friendly, as the entire model is specified in simple tables that can be easily updated and modified as needed. For these reasons, the use of DICE should be considered in the development of structured methodologies to facilitate BRA.

AUTHORS CONTRIBUTIONS

All of the authors participated in the preparation of the article and approved the final version of the manuscript. H.A. and J.J.C. created the DICE version and ran the analyses. B. Bégaud acted as the academic PhD supervisor of this study.

DISCLOSURES

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APPENDIX

Table S1. List of Conditions used in the rotavirus vaccination DICE qBRm

Name	Definition
ID	Sequential number for each profile (auto)
Time	Mandatory system condition that tracks simulation time
TimeHorizon	User-selected duration of simulation
IntervNum	System, used when multiple interventions
StrategyVacc	Index of the current treatment (non-vaccination versus vaccination)
Age	Age at any time during execution
BsAgeDose1	Age at vaccine dose 1
Cohort	Birth cohort followed 5 years
CycleRVGE	User-selected duration of RVGE cycle
BsRvgeHospRate	Baseline RVGE hospitalisation rate
RvgeHospRate	RVGE hospitalisation rate according to time
NumHospRvge	Number of hospitalisations due to RVGE
NumDeathRvge	Number of deaths due to RVGE
RvgeFatalityRate	Case fatality rate for RVGE
CycleIS	User-selected duration of IS cycle
BsIsHospRate	Baseline IS hospitalisation rate
IsHospRate	IS hospitalisation rate according to time
NumHospIs	Number of hospitalisations due to IS
NumDeathIs	Number of deaths due to IS
IsFatalityRate	Case fatality rate due to IS
BsCoverage1	Vaccine coverage dose 1 at baseline
CurCoverage1	Vaccine coverage dose 1 according to time
Dose	Index of the current dose injection (Dose 1 versus Dose 2)
BsIsRR1	Relative risk of IS following dose 1 of rotavirus vaccination at baseline
CurIsRR1	Relative risk of IS following dose 1 of rotavirus vaccination according to time
BsRvgeRR1	Vaccine Effectiveness following dose1 of rotavirus vaccination at baseline
CurRvgeRR1	Vaccine Effectiveness following dose1 of rotavirus vaccination according to time
BsAgeDelayD1D2	Delay between dose 1 and dose 2
BsAgeDose2	Age at vaccine dose 2
BsRvgeRR2	Vaccine Effectiveness following dose2 of rotavirus vaccination at baseline
CurRvgeRR2	Vaccine Effectiveness following dose2 of rotavirus vaccination according to time
BsIsRR2	Relative risk of IS following dose 2 of rotavirus vaccination at baseline
CurIsRR2	Relative risk of IS following dose 2 of rotavirus vaccination according to time
RiskPeriod	Risk period of vaccine-induced IS following vaccination
BsCoverage2	Vaccine coverage dose 2 at baseline
CurCoverage2	Vaccine coverage dose 2 according to time
NextEventTime	System, keeps track of time for next event
NextEvent	System, keeps track of which event is next

IS, intussusception; RVGE, rotavirus gastroenteritis; DICE, discretely integrated condition event; qBRm, quantitative benefit-risk model.

Table S2. List of Events used in the rotavirus vaccination DICE qBRm

Name	Definition
Start	Initialise execution for intervention
RVGE	Occurrence of the RVGE
Intussusception	Occurrence of the IS
Vaccinate1	Initiate rotavirus vaccination
VaccineEff	Initiate vaccine effectiveness of rotavirus vaccination
VaccineRisk	Initiate IS risk following rotavirus vaccination
Vaccinate2	Complete rotavirus vaccination
End	End execution for intervention

IS, intussusception; RVGE, rotavirus gastroenteritis; DICE, discretely integrated condition event; qBRm, quantitative benefit-risk model.

Table S3. List of Outputs for each strategy used in the rotavirus vaccination DICE qBRm

Name	Definition
ctHospRvgeVacc	Number of RVGE hospitalisations following vaccination strategy
ctDeathRvgeVacc	Number of RVGE deaths following vaccination strategy
ctHospIsVacc	Number of IS hospitalisations following vaccination strategy
ctDeathIsVacc	Number of IS deaths following vaccination strategy
ctHospRvgeNoVacc	Number of RVGE hospitalisations following no vaccination strategy
ctDeathRvgeNoVacc	Number of RVGE deaths following no vaccination strategy
ctHospIsNoVacc	Number of IS hospitalisations following no vaccination strategy
ctDeathIsNoVacc	Number of IS deaths following no vaccination strategy
RepNum	System; Replication number

IS, intussusception; RVGE, rotavirus gastroenteritis; DICE, discretely integrated condition event; qBRm, quantitative benefit-risk model.