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2. **Zhang C**, Spence OM, Reeves G, dosReis S (2019, August) " Changes In The Population Characteristics Of U. S. Youth Receiving Psychotropic Polypharmacy: 1996 To 2016" *Podium*

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7. Qato DM, **Zhang C**, et al. (2018, November) "Non-medical co-use of opioids and other controlled substances among pregnant and non-pregnant women in the US: Findings from 2005-2014 National Survey on Drug Use and Health (NSDUH) data". *Orally presented* at American Public Health Association: APHA, San Diego, CA

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## Abstract

Title of Dissertation: Impact of Undertreatment of Depression on Suicide and Suicide Attempt among Children and Adolescents: A Simulation Study with Microsimulation and Agent-Based Models

Chengchen Zhang, Doctor of Philosophy, 2022

Dissertation Directed by: Susan dosReis, PhD, Pharmaceutical Health Services Research Department

**Background:** Depression is a strong risk factor for suicide, but undertreatment of depression is common among children and adolescents. The impact of undertreatment of depression on suicidal behaviors in this population is largely unknown due to the limitations of conventional data sources and methods. This dissertation research aims to overcome these challenges by using simulation models to answer two questions: 1) Is undertreatment of depression associated with increased risk of suicidal behaviors? 2) Do interventions that reduce undertreatment of depression lower the risk of suicidal behaviors?

**Methods:** A microsimulation model simulated the 1-year suicide rate and suicide attempt risk with 12-, 36-, 52-week antidepressant treatment and no treatment in children and adolescents with depression. Modified Poisson regression estimated the suicide rate ratios and suicide attempt risk ratios for 12-, 36- and 52-week treatment compared with no treatment. An agent-based model simulated the potential impact of the following interventions in preventing suicide and suicide attempt in a synthetic population of children and adolescents: 1) depression screening (i.e. reducing untreated depression); 2) reducing attrition during depression treatment (i.e., increasing the proportion who

complete the first 12 weeks of treatment); 3) suicide intervention (i.e., screen and treat individuals who need suicide care) among depressed individuals; 4) universal suicide intervention in medical settings.

**Results:** Compared with no treatment, 12-, 36- and 52-week antidepressant treatment was significantly associated with decreased suicide rate and risk of suicide attempt.

Depression screening could reduce the risk of suicide attempt (-0.64% (95% Credible Interval (CI): -1.13%, -0.11%)) only when 80% untreated depression was reduced.

Universal suicide intervention showed a significant decrease in the risk of suicide attempt, which increased with the screened proportion (20%: -0.68% (95% CI: -0.87%, -0.55%), 50%: -1.47% (95% CI: -1.61%, -1.77%), 80%: -2.89% (95% CI: -4.57%, -2.31%). The other interventions did not show a significant effect in reducing the risk of suicide attempt in the population.

**Conclusion:** Antidepressant treatment for at least 12 weeks may reduce risk of suicidal behaviors. Universal suicide intervention in medical care settings may be more effective in reducing suicidal behaviors compared with interventions that reduce undertreatment of depression.

Impact of Undertreatment of Depression on Suicide and Suicide Attempt among Children  
and Adolescents: A Simulation Study with Microsimulation and Agent-Based Models

by  
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Dissertation submitted to the Faculty of the Graduate School of the  
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## LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Definition</b>
ABM	Agent-based model
CBT	Cognitive behavior therapy
MDD	Major depressive disorder
CDC	The United States Centers for Disease Control and Prevention
NAASP	The National Action Alliance for Suicide Prevention
SD	System dynamics modeling
DES	Discrete event simulation
NEM	The Network Episode Model
CI	Credible intervals
MEPS	Medical Expenditure Panel Survey
NCSAS	National Comorbidity Survey – Adolescent Supplement
TADS	The Treatment for Adolescents with Depression Study
TORDIA	The Treatment of Resistant Depression of Adolescents Study
CDRS-R	Children’s Depression Rating Scale - Revised
ADHD	Attention-deficit hyperactivity disorder
CD/ODD	Conduct disorder/oppositional defiant disorder
BIC	Brief intervention and contact
USPSTF	The United States Preventive Services Taskforce
PHQ	Patient Health Questionnaire
ASQ	The Ask Suicide-Screening Questions
BSSA	Brief suicide safety assessment

SD	Standard deviation
OR	Odds ratio
SSRI	Selective serotonin reuptake inhibitors
AAP	American Academy of Pediatrics

## **1. Overview**

Depression is a strong risk factor for suicide, but many children and adolescents in the United States who are diagnosed with depression do not receive adequate care. No treatment or treatment that does not meet the guideline recommendations, i.e., undertreatment, for depression is common among young people.<sup>1-3</sup> This places them at risk for suicide. This dissertation investigated undertreatment of depression and incidence of suicide and suicide attempt among children and adolescents. The research focused on two key areas: 1) the relationship between undertreatment of depression and suicide among children and adolescents with depression; 2) the effects of interventions to reduce undertreatment of depression on lowering the risk of suicide and suicide attempt. Microsimulation and agent-based modeling (ABM) methods were used in this dissertation research to combine evidence from multiple sources in order to simulate the dynamic relationship between the disease course of depression and healthcare seeking behaviors in a synthesized population of children and adolescents.

### **1.1 Significance of the Problem**

Suicide among children and adolescents in the United States has increased by over 50% since 1999<sup>4</sup> and suicide was the second leading cause of death in this population.<sup>5</sup> Depression is the strongest risk factor for suicide which affects about 9% of children and adolescents in the United States.<sup>1</sup> Despite well-documented evidence of the efficacy of antidepressant and nonpharmacological (e.g. , psychotherapy, cognitive behavior therapy (CBT)) treatment for relieving symptoms of depression,<sup>6,7</sup> more than 60%<sup>1</sup> of children and adolescents who are diagnosed depression do not receive any treatment or counseling service from a mental health professional. Among those

diagnosed and ever treated, half do not receive adequate follow-up visits or duration of treatment.<sup>2,3</sup> Undertreatment of depression, including no treatment or treatment that does not meet guideline recommendations in terms of treatment duration, can lead to uncontrolled or worsened depressive symptoms and elevate the risk of suicide.<sup>8-10</sup> A large proportion of suicide decedents and people who attempted suicide have untreated depression at the time of suicide or suicide attempt.<sup>11</sup>

There is limited scientific evidence from controlled trials or observational cohort studies addressing the association between undertreatment of depression and suicide. Given ethical concerns, it is not possible to implement an experimental design to investigate the causal relationship in human subjects. An observational study design is also challenging given that suicide is a rare event, and so a long follow up and large sample size are needed to obtain a robust statistical inference.<sup>12</sup> Furthermore, suicidal behaviors are under-reported in secondary data<sup>4</sup> and most observational studies of suicidal behaviors lack rigorous controls.<sup>13</sup> The association between undertreatment of depression and suicide is mostly considered self-evident because a lower risk of suicidal ideation and suicide attempt is usually observed when depressive symptoms are lessened.<sup>14,15</sup>

These methodological challenges are exacerbated by the fact that suicide is a result of the interplay among societal, community, interpersonal and individual factors. Data sources that contain accurate records of suicide and comprehensive information on suicide risk factors are lacking. There is no single data source that is sufficient to investigate the relationship between depression treatment, and importantly receipt of adequate treatment, and suicide. Therefore, an approach that enables one to utilize a

range of information sources in a systematic way is needed to inform interventions and policy making to prevent suicide among children and adolescents. This dissertation utilized microsimulation and ABM methods to investigate the impact of undertreatment of depression on the risk of suicidal behaviors among children and adolescents.

Microsimulation is a computation-based simulation approach widely used in healthcare research to evaluate the contribution of independent risk factors on a health outcome in the absence of empirical data.<sup>16</sup> ABM is a method similar to microsimulation except that ABM allows one to simulate agents' interactions between each other as well as with the environment. Increasingly, ABM has been used in clinical and public health research<sup>17,18</sup> as an alternative to clinical trials for causal inference.<sup>19</sup> It is used to compare the outcomes of different public health interventions.<sup>20,21</sup> Using microsimulation and ABM methods, this dissertation research was able to synthesize evidence from multiple data sources to simulate the care process over the course of depression treatment and the incidence of suicidal behaviors during the process of care. In this way, we were able to investigate the relationship between undertreatment of depression and suicide and evaluate population-level effects of different suicide prevention strategies.

## **1.2 Scientific Premise**

The scientific premise for investigating the impact of undertreatment of depression on suicide is based on the well-established evidence and prior research showing that 1) depression is a strong risk factor for suicide.<sup>22,23</sup> and 2) evidence-based depression treatment is efficacious in reducing depressive symptoms.<sup>6,7</sup> Although the etiology of suicide is still unclear, prior research has demonstrated that people are at

greatest risk of suicide during major depressive episodes.<sup>24</sup> This is the conceptual basis for this dissertation research.

### **1.3 Central Hypothesis, Research Questions and Specific Aims**

The central hypothesis is that undertreatment of depression increases the risk of suicidal behaviors among children and adolescents. The study was designed to answer two specific research questions: 1. Is undertreatment of depression associated with risk of suicidal behaviors among children and adolescents? 2. Will the suicide rate and risk of suicide attempt decrease if the undertreatment of depression among children and adolescents is reduced?

To answer the research questions, this dissertation research was guided by the following three specific aims:

**Aim 1:** Investigate the relationship between undertreatment of depression and suicide among children and adolescents with major depressive disorder (MDD), overall and by age and sex subgroups.

**Aim 2:** Develop an ABM to simulate the dynamics of course of depression and the healthcare seeking behaviors in a population of children and adolescents.

**Aim 3:** Estimate the hypothetical impact of interventions that reduce undertreatment of depression on preventing suicide among children and adolescents.

### **1.4 Impact on the Field**

This dissertation addressed an important public health issue and used advanced scientific methods for suicide-related research among children and adolescents. Findings

from this dissertation research fill a gap in knowledge of the relationship between undertreatment of depression and suicide and provide evidence for potential population effects of interventions to reduce undertreatment of depression on preventing suicide. Prevention of suicide in children and adolescents is critical because onset of suicidal thoughts and suicide attempts mostly occurs by the mid-twenties<sup>25</sup> and successful intervention early in life may potentially save more years of life. The dissertation research utilized computation-based simulation (i.e., microsimulation and ABM) to synthesize information from multiple information sources to account for multiple risk factors associated with suicidal behaviors and individuals' care seeking behaviors. There is only limited application of microsimulation and ABM in the field of suicide research. This dissertation provides a pragmatic example of implementing system science methods that can inform future research and identify research priorities for suicide prevention.

## **2 Introduction**

### **2.1 Background**

#### **2.1.1 Overview of Suicide, Suicide Attempt and Suicidal Ideation among Children and Adolescents**

Suicidal behaviors, including suicide, suicide attempt and suicidal ideation, are a major public health concern that causes death and disability. The United States Centers for Disease Control and Prevention (CDC) defined three types of suicidal behaviors:<sup>26</sup> 1) suicide, which is death caused by self-injurious behaviors with intent to die; 2) suicide attempts, which include nonfatal self-injurious behaviors with intent to die; 3) suicidal ideation, which is thinking of or planning suicide. Although suicidal behaviors are prevalent in all age groups, they are particularly concerning for young people. In the United States, suicide is the second leading cause of death for children and adolescents aged 10 to 18 years old and accounts for more than 33% of deaths in this age group.<sup>5,27</sup> Prevalence of suicide attempts and suicidal ideation are much higher among adolescents compared to other age groups.<sup>28</sup> In 2019, 18.8% of high school students had seriously considered suicide, 15.7% of them made a suicide plan and 8.9% attempted suicide at least once in the past 12 months.<sup>27</sup> Interventions to prevent suicidal behaviors among children and adolescents can have a significant impact on preventing death and disability and in saving more years of life.

Previous research identified several factors that influence suicide risk. The key risk factors for suicide include gender, family history of suicidal behaviors, previous suicide attempt, early stressful life events (e.g., childhood maltreatment, parental suicide,

and bullying), mental disorders, substance abuse, physical illness, and access to lethal means.<sup>29</sup> Mental disorders, especially depression, bipolar disorder, schizophrenia, and anxiety, have the strongest association with suicidal behaviors among young people.<sup>22,23</sup> Psychological autopsy studies report that over 90% of youth suicide decedents have mental disorders.<sup>30</sup> It is believed that suicidal behaviors are rarely caused by a single risk factor,<sup>31</sup> however, current knowledge of the etiology of suicide is insufficient to clarify the pathways through which suicidal behaviors emerge. Psychological models mostly consider suicidal behaviors as a result of the influence from a series of stressors, individuals' ability to adapt to stress and personal impulsivity.<sup>32</sup> For example, the interpersonal theory of suicide explains suicidal behaviors as an outcome of the interplay of social isolation, life events, physical illness, and capability of conducting suicide.<sup>33</sup>

Suicide is a preventable cause of death. Preventive interventions are thus critical given the increasing number of suicidal behaviors in youth over time.<sup>34</sup> Interventions for primary prevention usually aim to prevent the onset of suicidal ideation and behaviors. For example, healthcare providers can be trained to foster children and adolescents' ability to cope with frustration<sup>35,36</sup> and teach them to actively seek support, establish peer and family connectedness, and engage in mental health treatment.<sup>37-39</sup> Intervening on the parents' mental conditions is another approach of primary prevention.<sup>35,36</sup> Parental mental health has a strong influence on child mental health.<sup>40,41</sup> Children's suicidal symptoms can be relieved with mitigation of their parents' mental disorders.<sup>42</sup> Secondary prevention focus on intervening the risk factors of suicidal behaviors, which include mental illness, substance abuse, family history of suicide, social isolation and hopelessness.<sup>37,43,44</sup> Evidence from prior research supports that treating mental health

conditions with psychotropic medication and psychosocial interventions reduces suicidal ideation and behaviors.<sup>45</sup> Tertiary prevention typically focuses on preventing possible future suicidal behaviors after a suicide attempt.

Most individuals at increased suicide risk experience multiple adversity at the same time, which requires systematic approaches that generate a more supportive and suicide-aware environment.<sup>34</sup> In 2012, the National Action Alliance for Suicide Prevention (NAASP) updated the National Strategy for Suicide Prevention and encouraged a systematic strategy which enforces workforce training, promotes identification of suicide risk and use of evidence-based treatment, encourages patients' engagement, and strengthens continuity of care delivery to achieve the goal of reducing suicide.<sup>46</sup>

### **2.1.2 Depression and Suicidal Behaviors**

Depression is a prevalent psychiatric disorder that affects 9% of youths in the U.S..<sup>28</sup> Depression can occur at any age, but most individuals are first diagnosed with depression in adolescence or early adulthood.<sup>47-49</sup> Younger age of onset is associated with a higher risk of recurrent episodes of depression and worse functional impairment.<sup>50,51</sup> Some individuals may spontaneously recover from an acute episode of depression without any treatment, but 80% will suffer from at least one recurrent episode and have significant residual symptoms after initial depression diagnosis.<sup>52-54</sup> Other factors that contribute to recurrence of depressive episodes include severity of the initial episode, presence of psychiatric comorbidities, and lack of adequate treatment.<sup>55</sup>

The efficacy of pharmacological and nonpharmacological treatment in controlling depressive symptoms has been well documented,<sup>6,7</sup> but undertreatment remains a common problem among both pediatric and adult populations.<sup>56-58</sup> Depression treatment usually consists of at least two stages: acute phase (i.e., the first 8-12 weeks of treatment) and continuation phase (i.e., the 6-months treatment after the acute phase).<sup>59</sup> However, less than half of youths are adherent in the acute phase, and 21% are adherent across both acute and continuation treatment phases as is guideline-recommended.<sup>2</sup> Among adolescents who initiated depression treatment, 40% -70% do not have follow-up care or symptom assessment in the first three months.<sup>56,60</sup> In addition to poor adherence, delay and failure to seek treatment also contribute to undertreatment. More than 60% of youths diagnosed with depression do not receive any treatment or counseling service from a mental health professional.<sup>28</sup> Poor adherence to treatment, delay in treatment initiation, and untreated depression could potentially lead to uncontrolled depressive symptoms and thereby increase the risk of suicide.

Depression is a major risk factor of suicide. The risk of suicide among those with depression can be as high as 17 times that in general population.<sup>61</sup> One half to two-thirds of suicide decedents have depression at time of death.<sup>30,62</sup> Studies of suicide among children and adolescents are quite limited. Some prospective cohort studies based on adults show that about 10-12% of those with depression die by suicide during follow-up.<sup>63,64</sup> Suicidal ideation and suicide attempt mostly occur during the ongoing episodes of depression and typically abate when depressive symptoms are alleviated.<sup>14,15,65,66</sup> Severe and chronic depression are more likely associated with the risk of suicidal behaviors.<sup>67,68</sup> Although the potential causal relationship between depression and suicidal behaviors

seems self-evident, controlled clinical trials and cohort studies are still limited in providing sound evidence for the effect of an adequate course of treatment for depression on suicidal behaviors in a population of children and adolescents. Several clinical trials reported decreased suicidal behaviors after 12-36 weeks of antidepressant treatment,<sup>69-71</sup> but these studies have limited generalizability due to a small sample size, exclusion of people considered high suicide risk, and short follow-up.

### **2.1.3 Dynamic Simulation Modeling and Public Health**

A complex system is by defined a system that involves interactions among entities (e.g., patients and healthcare providers in a healthcare system) and exhibit features like emergence (i.e., properties of the system that are different from properties of entities), feedback (i.e., a change that may reinforce or hamper further changes) and adaption (i.e., behavior adjustment in response to interventions on the system).<sup>72,73</sup> The public health system is considered a complex system which includes multiple interacting entities that lead to different health outcomes in the population. This makes decision-making in public health challenging because the potential impact of an intervention can be difficult to predict solely based on the characteristics of the entities (e.g., individuals) at baseline. Over the past decade, complex system approaches have been increasingly endorsed and used to investigate population health problems in infectious diseases, noncommunicable diseases, health behaviors and social epidemiology.<sup>18</sup> Dynamic simulation modeling is a group of computation-based methods, including system dynamics modeling (SD), discrete event simulation (DES), microsimulation and ABM, and have been widely used to simulate health care systems and to evaluate systematic interventions.<sup>73</sup> These methods also supplement to epidemiologic methods when an empirical study in the population is

not feasible or data required to study the question lacks.<sup>74</sup> Dynamic simulation modeling methods have unique advantages such as testing different assumptions,<sup>16</sup> investigating causal-relationships,<sup>19</sup> and identifying optimal interventions in complex systems.<sup>20</sup>

Microsimulation and ABM create individual-level models. The past decade has seen growing interest in applying microsimulation and ABM to investigate different population health problems, including to examine distribution of risk factors of population health, to assess the contribution of risk factors in disease prevalence, and to predict intervention effects on population health.<sup>16,75</sup> ABM simulates dynamic behaviors of agents (e.g., individuals) with a set of characteristics that interact among themselves and with the environment based on a series of predefined rules.<sup>76,77</sup> Microsimulation is generally similar to ABM except that microsimulation assumes independence among agents while ABM allows one to simulate interactions among and between agents and the environment. ABM has been used in clinical and public health research<sup>17,18</sup> as an alternative to clinical trials for causal inference.<sup>19</sup> It also provides an approach to compare potential impact of different public health interventions.<sup>20,21</sup>

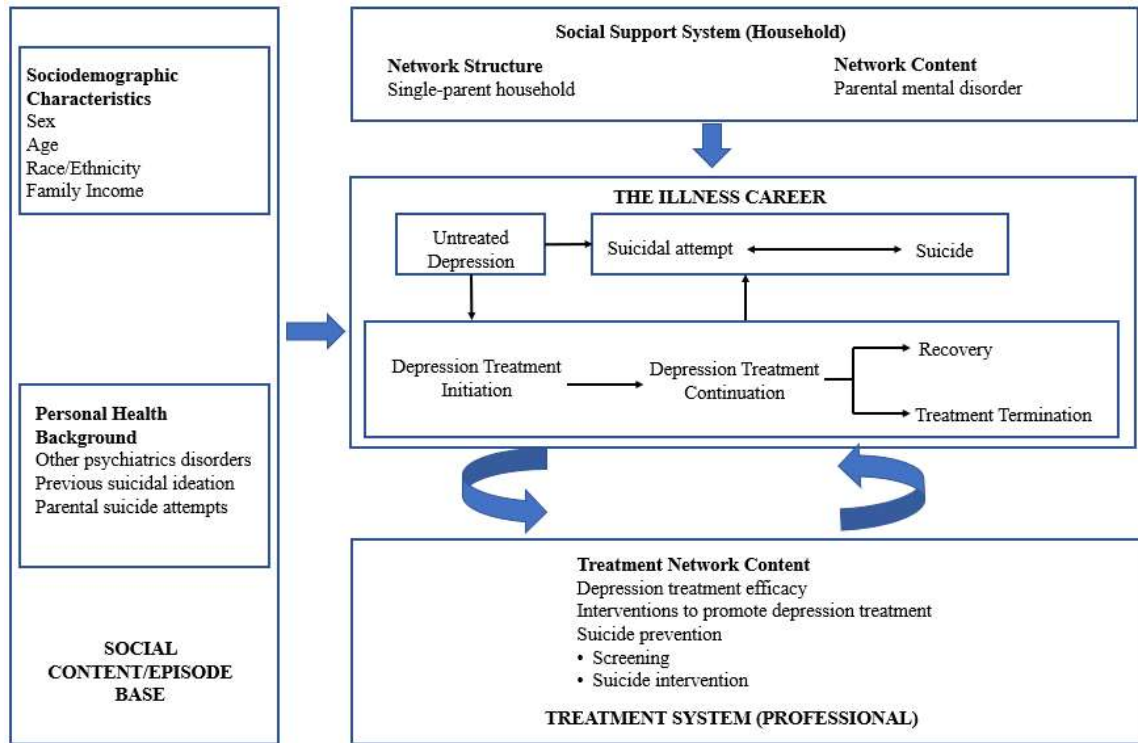
#### **2.1.4 Key Gaps the Research Fills**

This dissertation research contributes to advancing scientific evidence to address two main gaps: 1) the relationship between undertreatment of depression and suicidal behaviors is limited due to the low base-rate of suicide in the population and lack of data on accurate records of suicide events and comprehensive information on suicide risk factors; 2) the population-level effect of interventions to reduce undertreatment of depression on preventing suicidal behaviors in children and adolescents.

## 2.2 Theoretical Framework

The Network Episode Model (NEM) is a theory proposed by Pescosolido<sup>78</sup> that illustrates how individuals' social networks influence mental health service use and patients' compliance throughout the course of illness. The NEM incorporates previous theories for health service utilization including the social-behavior model<sup>79</sup> and the Health Belief Model<sup>80</sup> to elucidate the relationships between social context and health belief with health seeking behaviors. What is unique about the NEM is that it conceptualizes health service utilization as patterns that may change over time. According to the NEM, mental healthcare utilization is not a fixed, one-time decision, but changes based on individuals' interactions with their social networks during the progress of illness (i.e., illness career).<sup>81</sup> The NEM has four components. The social content forms the base of the model, which is described by sociodemographic, clinical and geographic characteristics of individuals and their social networks that will influence the trajectory of illness. The social support system and the treatment system represent a set of social networks that individuals rely on when making medical decisions. The illness career conceptualizes critical points where individuals decide whether or not to seek, initiate, comply with or terminate healthcare. The illness career and social networks are dynamic and interact at various critical points.<sup>81</sup>

**Figure 2.1** The Theoretical Framework of the Dissertation Research Developed Based on The Network Episode Model



The NEM is selected as the theoretical framework in this study to account for the dynamic nature of the care-seeking behaviors in the population (Figure 2.1). Treatment for depression is not a one-time visit, but has to be implemented recurrently and adjusted according to patients' response.<sup>59</sup> Therefore, patterns of depression treatment are actually formed based on a series of sessions in which individuals make a decision whether to initiate, continue or discontinue the treatment based on their characteristics at that session. The NEM provides a framework that allows one to model such dynamics of depression treatment.

### **3 Aim 1: Impact of Duration of Antidepressant Treatment on Suicide and Suicide Attempt Among Children and Adolescents with Major Depressive Disorder: A Microsimulation Study**

#### **3.1 3.1 Abstract**

**Background:** Depression is a major risk factor for suicide, yet it is common for children and adolescents to drop out before completing the recommended treatment duration. Data sources to fully address risk factors for suicide are lacking. An approach that utilizes information from different sources is needed to generate evidence of the impact of depression treatment duration on suicide risk.

**Objective:** To estimate the potential impact of antidepressant treatment duration on suicidal behaviors among children and adolescents with MDD.

**Methods:** A microsimulation model informed by clinical trials and national survey data simulated suicide risk during the course of depression in a synthetic child and adolescent population with MDD. Antidepressant treatment with different duration was examined: 52-, 36-, 12-week treatment and no treatment. The 1-year suicide rate and suicide attempt risk in the overall population and by age and sex subgroups were estimated for each treatment duration. Modified Poisson regression estimated the suicide rate ratios and suicide attempt risk ratios for 52-, 36- and 12-week treatment compared with no treatment.

**Results:** The 1-year suicide rate was 74 (95% Credible Interval (CI): 64, 84), 75 (95% CI: 66, 85), 90 (95% CI: 79, 103), and 117 (95% CI: 101, 128) per 100,000 for 52-, 36-, 12-week treatment and no treatment, respectively. Compared with no treatment, the

suicide rate ratio was 0.6 (95% CI: 0.5, 0.7), 0.7 (95% CI: 0.4, 0.9), and 0.8 (95% CI: 0.6, 1.2) for 52-, 36- and 12-week treatment, respectively. The 1-year suicide attempt risk was 12.1% (95% CI: 12.0%, 12.2%), 12.4% (95% CI: 12.3%, 12.5%), 15.0% (95% CI: 14.9, 15.1%), and 22.2% (95% CI: 22.1%, 22.3%) for 52-, 36-, 12-week treatment and no treatment, respectively. Relative to no treatment, the risk ratio was 0.6 (95% CI: 0.5, 0.6), 0.6 (95% CI: 0.5, 0.6) and 0.7 (95% CI: 0.6, 0.8) for 52-, 36- and 12-week treatment, respectively. The suicide rate and suicide attempt risk were lower in ages 10-12 than that in ages 13-18. Males had a lower risk of suicide attempt but higher suicide rate than females.

**Conclusion:** Longer duration of antidepressant treatment can reduce suicidal behaviors among children and adolescents with MDD. At least 36-weeks of treatment can maximize suicide risk reduction.

### 3.2 Introduction

Depression is one of the strongest risk factors for suicide and affects about 9% of children and adolescents in the U.S.<sup>28</sup> The risk of suicide among those with depression can be as high as 17 times that in general population.<sup>61</sup> About 60% to 90% suicide decedents are found to have depression.<sup>30,62</sup> Previous studies have shown that relief of depressive symptoms are associated with abated suicide risk,<sup>14,15,65-68</sup> therefore, it can be theorized that treatment of depression can prevent suicide. The current practical guidelines of depression treatment for children and adolescents have suggested a strategy that consists of a 3-month acute-phase treatment followed by at least 6 months of continuation-phase treatment with evidence-based therapy (i.e., antidepressant, CBT or combined therapy) to induce remission, and 1 year of maintenance-phase treatment to prevent relapse.<sup>59,82</sup> However, undertreatment that does not follow the recommendations is common. Previous studies found more than half of children and adolescents in Medicaid discontinued antidepressant treatment within 3 months of treatment initiation.<sup>2</sup> More than 60% of children and adolescents with depression do not receive any treatment or counseling service from a mental health professional.<sup>1</sup> Undertreatment of depression may potentially lead to uncontrolled depressive symptoms, thereby placing children and adolescents at elevated risk of suicide.

Given the seemingly self-evident causal relationship between undertreatment of depression and suicide, it would follow that promoting depression treatment that follows the recommendations would be a potentially effective approach to prevent suicide among children and adolescents with MDD. However, scientific evidence examining the relationship between undertreatment of depression and suicide is limited. With a low

base-rate in the population, suicide study requires a large sample size to ensure statistical reliability, which is usually hard to obtain.<sup>12</sup> Another challenge for suicide research is lack of data sources that contain accurate records of suicide and comprehensive information on suicide risk factors. Administrative claims data allows one to enroll larger samples and have longer follow-up duration, but claims data usually lack sociodemographic characteristics that are critical to study suicidal behaviors and may underestimate suicidal outcomes in the population due to under-coding of suicide.<sup>83,84</sup> Some national surveys collect comprehensive information on suicide risk factors, but are typically limited to cross-sectional estimates.<sup>85,86</sup> There is no single data source that is sufficient to investigate the relationship between depression treatment, and importantly receipt of adequate treatment, and suicide. Therefore, a better approach that enables us to utilize information from different sources in a systematic way is needed to inform interventions and policy making to prevent suicide among children and adolescents.

Microsimulation is a computation simulation method that provides an alternative approach to causal inference.<sup>87</sup> Researchers can conduct virtual experiments to examine the population-level effects of different interventions by altering the input parameters with multiple simulation runs. Since each simulation is run on the same population, the model outcomes can be viewed as analogous to potential outcomes obtained from counterfactual states. The microsimulation model developed in this study utilized multiple data sources to account for sociodemographic and clinical characteristics associated with suicidal behaviors. We examined the suicide rate and risk of suicide attempt in the synthesized population of children and adolescents with MDD when they received antidepressant treatment of different duration. The central hypothesis of this

study that increasing duration of antidepressant treatment is associated with decreased risk of suicidal behaviors.

### **3.3 Methods**

A microsimulation model was developed to simulate the occurrence of suicidal ideation, suicide attempt and completed suicide throughout the course of depression among children and adolescents with MDD. The synthetic population formed a closed cohort where no additional agents entered during the model process. The time-horizon for the model is 1 year (52 weeks). Each time step in a simulation run represents one week. Parameters for the microsimulation model were derived from several key data sources. Medical Expenditure Panel Survey (MEPS, 2016-2018) and the National Comorbidity Survey – Adolescent Supplement (NCSAS) were used to obtain sociodemographic and clinical characteristics of children and adolescents with MDD. Published results of the Treatment for Adolescents with Depression Study (TADS)<sup>69,88,89</sup> and the Treatment of Resistant Depression of Adolescents (TORDIA) study<sup>90–92</sup> were referred to for change of depressive symptoms and suicidal ideation associated with depression therapies. Suicide rate in children and adolescents was obtained from the CDC Fatal Injury Report.<sup>5</sup> We extrapolated the model parameters that were not available in above sources from published literature. All model parameters and the corresponding sources are listed in Appendix 8.2.

#### **3.3.1 Agent Population**

We initialized 300,000 agents aged 10-18 to synthesize a nationally representative sample of children and adolescents with MDD. A baseline Children’s Depression Rating Scale -Revised (CDRS-R) score ranging from 35 to 113 was assigned to each agent.

Severity of depressive symptoms was categorized based on CDRS-R score according to cut-off points used in previous clinical trials and published literature<sup>93,94</sup>: 1) CDRS-R score between 35 to 60 defined mild to moderate depression; 2) CDRS-R score above 60 defined severe depression.

Sociodemographic characteristics of the agents included age, sex, race/ethnicity, family income, single or no-parent household. The clinical characteristics potentially associated with suicidal behaviors included other psychiatric disorders (i.e., attention-deficit hyperactivity disorder (ADHD), bipolar disorder, conduct disorder/oppositional defiant disorder (CD/ODD), and alcohol/drug abuse), prior history of suicidal ideation, and parental suicide or suicide attempt.<sup>29</sup> The characteristics assigned to agents reflected the distributions in the national population of children and adolescents with MDD estimated based on MEPS and the NCSAS. Details of the characteristics' assignment are described in Appendix 8.1.1.1.

### **3.3.2 Model Course**

#### *Depressive Symptoms Change*

During the 52-week model course, agents' depressive symptoms changed over time as reflected by the CDRS-R scores. The CDRS-R scores were set to change as a linear function of the natural log of days from baseline,<sup>95</sup> which consists of three parameters: the intercept that represents an agent's baseline CDRS-R score, the coefficient that represents unit change of an agent's CDRS-R scores with the natural log of days, and the random error term. To account for the variability of individual trajectories of depressive symptoms change, the coefficients for the natural log of days were generated based on mixed effects models, where the coefficients of all agents

followed a distribution with a certain mean (i.e., fixed effect) and variance (i.e., random effect). The mean and variance were extrapolated from the TADS and TORDIA studies (for treatment-resistant agents only).<sup>91,95,96</sup> For each agent, different coefficients were assigned to represent his/her CDRS-R score change corresponding to the treatment status (i.e., receiving treatment or not, or switched to other therapies if being treatment-resistant) in a time-step. Additional details for function parameterizing are described in Appendix 8.1.2.2.

A decrease of 33% or more in CDRS-R score from baseline to Week 12 was used to define response to the treatment in this study. The threshold was determined through calibration to have a model-estimated remission rate at Week 12 closed to the empirically observed values (Appendix 8.3).

#### *Remission and Relapse*

Agents were considered remitted, i.e., no longer displaying clinical symptoms, if CDRS-R scores fell below 28.<sup>97</sup> Agents who remained remitted for 8 consecutive weeks were considered recovered.<sup>88</sup> Relapse was a recurring depressive episode among remitted or recovered agents. In the microsimulation model, relapse was modeled as setting the CDRS-R scores of the remitted or recovered agents increase to a random value ranging from 35 to 113, which was a threshold for depression diagnosis.<sup>94</sup> The probability of relapse was extrapolated from published literature ( Appendix 8.2).

#### *Suicidal Events*

Suicidal events included suicidal ideation, attempt, and completed suicide. These events could occur at each time step.

Suicidal ideation was defined as a binary variable in the model to indicate whether an agent had suicidal ideation or not in the time step. The probability of having suicidal ideation was determined based on agents' sociodemographic characteristics, depression severity, psychiatric comorbidities, and parental suicide or suicide attempt with a logistic regression model estimated based on NCSAS (Appendix Section 8.1.2.3).

The probability of suicide attempt was re-assigned at each time step based on agents' suicidal ideation and MDD recovery status. The probability of suicide attempt and the corresponding sources to extrapolate it are listed in Appendix Section 8.2.

The probability of completed suicide was re-assigned to agents at each time-step based on agents' age, sex, suicidal ideation status, previous suicide attempt and MDD recovery status. Suicide rates by age, sex and MDD recovery status without previous suicidal ideation or suicide attempt were calculated using Bayesian formula, with necessary information estimated from MEPS data (the estimated of prevalence of MDD), CDC Fatal Injury Report (the estimate of suicide rate in children and adolescents), and published psychological autopsy studies (the estimate of prevalence of MDD among children and adolescents who completed suicide).<sup>30,98</sup> Probability of completed suicide following suicidal ideation or suicide attempt were assumed to increase by 3-4 times based on previous report on the association between suicidal ideation, suicide attempt and suicide<sup>99</sup> (Appendix Section 8.2).

The details of determining the probability of suicide attempt and suicide are discussed in Appendix Section 8.1.2.3.

### **3.3.3 Model Calibration**

The purpose of calibration is to ensure that the model generates valid results close to what is observed in the real world. This is accomplished by adjusting the input model parameters that cannot be directly estimated from available data sources. Assuming that efficacy and safety of depression therapies observed in clinical trials were representative of those in a national population, the calibration was conducted to the following model-produced results against results reported in TADS and TORDIA studies:<sup>69,90</sup> 1) decrease of suicidal ideation from baseline to Week 12 after treatment; 2) response rate to antidepressant treatment at Week 12; 3) remission rate at Week 12 with antidepressant treatment; 4) remission rate at Week 36 with antidepressant treatment. Details of calibration process are included in Appendix 8.1.3.

### **3.3.4 Antidepressant Treatment Experiments**

In this study, we examined 0, 12-week, 36-week and 52-week antidepressant treatment for depression, which represent different levels of treatment from no treatment at all (0-week) to full adequacy of treatment (52-week). The hypothesis of the study is that increasing duration of antidepressant treatment is associated with decreased risk of suicidal behaviors (i.e., suicide rate and risk of suicide attempt).

The 52-week treatment followed the recommendations and included acute-, continuation-, and maintenance-phase treatment.<sup>59,82</sup> In the model, agents received antidepressants during the first 12 weeks of treatment (acute-phase treatment). The agents that responded to the treatment by Week 12 continued antidepressant treatment during continuation-phase treatment (i.e., Week 13- 36). Those remitted by Week 36 would continue the maintenance-phase treatment until the end of the model course (Week 52).

Since not all agents remitted by Week 36, we allowed unremitted agents to continue the treatment after Week 36 until remission, death or end of the model course.

Agents who did not respond to the antidepressant treatment by Week 12 were considered treatment-resistant and switched to another therapy (i.e., could be another antidepressant, augmentation, combined CBT with antidepressants) since Week 13, and continued the treatment through continuation-phase treatment. Treatment-resistant agents that remitted by Week 36 would continue the maintenance-phase treatment until the end of the model course (Week 52), while those that did not remit by Week 36 continued the treatment until remission, death or end of the model course.

In 12- and 36-week treatment, agents received antidepressants only for the first 12 or 36 weeks, and no treatment during the rest of the weeks until the end of the model course. In 0-week treatment (no treatment), agents received no treatment during the 52-week model course.

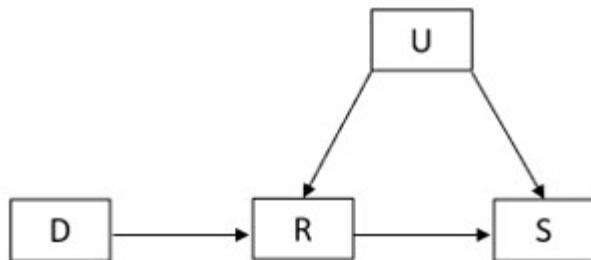
Using the calibrated model, experiments were conducted to evaluate the suicide rate and risk of suicide in the synthetic population when they received different duration of antidepressant treatment.

### **3.3.5 Sensitivity Analysis**

In this study, we calibrated the model under an assumption that the efficacy and safety of antidepressant treatment observed in clinical trials (i.e., response rate, remission rate, suicidal ideation reduction) were representative of those in a national population. However, a clinical sample is usually not fully representative of the national sample. If the unmeasured discrepancy between the two samples confounded the relationship of

depression treatment and suicidal behaviors, bias may be introduced in the model estimates. To assess the potential bias of parameterizing the model based on multiple data sources, we conducted a sensitivity analysis on the suicide rate ratios comparing the 52-week treatment with no treatment in a hypothetical setting where discrepancy between the clinical sample and the synthesized population may confound the relationship between response rate and risk of suicide (Figure 3.1).

**Figure 3.1** An Example of the Influence of the Discrepant Subgroup in the Population on the Estimate of Suicide Rate<sup>a</sup>



- a. D refers to depressive symptoms change.  
 R refers to response rate to depression treatment.  
 S refers to suicide in the population. U refers to the discrepant subgroup in the population.

We defined a binary variable U to represent the discrepancy between the clinical sample used for calibration and the synthesized population. Agents with U (i.e.,  $U = 1$ ) represented the subgroup that was not representative with the clinical sample (i.e., the discrepant subgroup). The response rate in this discrepant subgroup could be lower (20%) or higher (80%) than that in the non-discrepant subgroup (i.e., agents with  $U = 0$ ). The probabilities of completed suicide in the discrepant subgroup could be 0.25, 0.5, 1, 2 and 4 times that in the non-discrepant subgroup. The impact of U was tested assuming a low (25%), moderate (55%) or high (85%) prevalence of the discrepant subgroup, respectively. Under each prevalence, simulations with different combinations of response

rate and probability of completed suicide were run. We assessed how suicide rate ratios comparing 52-week treatment with no treatment in the synthetic population changed under each of the scenarios.

### **3.3.6 Statistical Analysis**

The 1-year suicide rate and risk of suicide attempt were estimated for overall agents and subgroups by sex and age.

The modified Poisson regression model was applied to estimate the suicide rate ratio and the risk ratio of suicide attempt comparing different treatment strategies based on the simulated data. The data generated from the microsimulation model was organized into a long dataset where agents simulated for each treatment strategy were stacked and flagged as different treatment groups: 1) 52-week treatment group; 2) 36-week treatment group; 3) 12-week treatment group; 4) no treatment group. Completed suicide or suicide attempt was included as the dependent variable and the treatment groups were included as the independent variable. The modified Poisson regression analysis was also conducted by age and sex subgroups.

The microsimulation model was repeated 100 times and each repetition produced its estimates on suicide rate, risk of suicide attempt, suicide rate ratios and risk ratios of suicide attempt. The median and 95% credible intervals (CIs) for all results were reported. The 95% CIs were calculated as the 2.5<sup>th</sup> and 97.5<sup>th</sup> rank of the 100 estimates. Repast Symphony 2.8 was used to build the microsimulation model and SAS 9.4 to conduct statistical analyses on the simulated data.

### 3.4 Results

The summary of baseline characteristics of agents is listed in Appendix Section 8.3. Table 3.1 summarizes the calibrated model results.

**Table 3.1** Model-Estimated Results Calibrated Against Empirically Observed Values

		Model Estimated Results (95%CI)	Empirically Observed Values
Response Rate	Week 12	60.52% (60.43%, 60.62%)	61% <sup>a</sup>
Remission Rate	Week 12	23.68% (23.60%, 23.78%)	24% <sup>a</sup>
	Week 36	54.16% (54.03%, 54.28%)	55% <sup>a</sup>
Suicidal Ideation	Baseline	41.93% (41.78%, 42.07%)	41% <sup>b</sup>
	Week 12	16.29% (16.20%, 16.38%)	16% <sup>c</sup>

- a. Extracted from the Treatment of Adolescent Depression Study (TADS) trial fluoxetine arm.
- b. Directly estimated using National Comorbidity Survey-Adolescent Supplement.
- c. The observed decrease in suicidal ideation is about 60% decrease from baseline, which is 16% compared with 41% at baseline.

#### *Risk of Suicide and Suicide Attempt Under Different Treatment Strategies (Primary Analysis)*

The simulated 1-year suicide rate and risk of suicide attempt for different treatment strategies are displayed in Table 3.2. The 1-year suicide rate was 117 (95% CI: 101, 128) per 100,000 if the agents received no treatment throughout the model course. The suicide rate decreased with increasing weeks of treatment: 90 (95% CI: 79, 103), 75 (95% CI: 66, 85), and 74 (95% CI: 64, 84) per 100,000 if they received 12-week, 36-week and 52-week treatment, respectively (Table 3.2). The suicide rate ratio comparing 52-week treatment with no treatment was 0.63 (95% CI: 0.45, 0.72), and increased to 0.65 (95% CI: 0.44, 0.90) and 0.78 (95% CI: 0.58, 1.15) when agents received 36-week

and 12-week treatment, respectively. There were 22.2% (95% CI: 22.1%, 22.3%) of agents that attempted suicide if they received no treatment throughout the model course. This number decreased to 15.0% (95% CI: 14.9, 15.1%), 12.4% (95% CI: 12.3%, 12.5%), and 12.1% (95% CI: 12.0%, 12.2%) if the agents received treatment for 12, 36, and 52 weeks, respectively. The risk ratio of suicide attempt comparing 52-week treatment with no treatment was 0.55 (95% CI: 0.51, 0.56), and increased to 0.56 (95% CI: 0.52, 0.57) and 0.68 (95% CI: 0.62, 0.69) for 36 and 12 weeks of treatment, respectively.

**Table 3.2** 1-year Risk of Suicide and Suicide Attempt for Different Duration of Antidepressant Treatment

Duration of Treatment	Suicide Rate (per 100000) (95% CI <sup>a</sup> )	Suicide Attempt Risk (%) (95% CI)	Suicide Rate Ratio (95% CI)	Suicide Attempt Risk Ratio (95% CI)
No Treatment (0-week Treatment)	116.50 (101.00, 128.33)	22.19 (22.06, 22.31)	1.00	1.00
12-week Treatment	90.17 (79.00, 102.67)	15.00 (14.88, 15.12)	0.78 (0.58, 1.15)	0.68 (0.62, 0.69)
36-week Treatment	74.50 (66.00, 85.00)	12.41 (12.29, 12.51)	0.65 (0.44, 0.90)	0.56 (0.52, 0.57)
52-week Treatment	73.50 (64.00, 83.67)	12.09 (12.00, 12.18)	0.63 (0.45, 0.72)	0.55 (0.51, 0.56)

a. 95% CI: 95% credible interval.

The suicide rate and risk of suicide attempt by sex and age (10-12 years old, 13-18 years old) groups are shown in Table 3.3 and Table 3.4, respectively. The suicide rates among females and children (10-12) were lower than those among males and adolescents (13-18). The risk of suicide attempt in females and adolescents was higher than that in males and children. The suicide rate ratios, comparing 12, 36, and 52 weeks of treatment with no treatment were similar with those in overall agents for both sex groups and adolescents. All suicide rate ratios in children were not significant. The risk ratios of

suicide attempt comparing 12, 36 and 52 weeks of treatment with no treatment in all subgroups were also similar with those in overall agents.

**Table 3.3** 1-year Risk of Suicide and Suicide Attempt for Different Duration of Antidepressant Treatment by Sex

Duration of Treatment	Suicide Rate (per 100000) (95% CI <sup>a</sup> )	Suicide Attempt Risk (%) (95% CI)	Suicide Rate Ratio (95% CI)	Suicide Attempt Risk Ratio (95% CI)
<b>Male</b>				
No treatment (0-week treatment)	192.49 (164.71, 221.13)	19.18 (18.94, 19.34)	1.00	1.00
12-week treatment	148.07 (127.71, 178.18)	12.58 (12.33, 12.70)	0.79 (0.63, 0.94)	0.66 (0.65, 0.67)
36-week treatment	124.46 (105.44, 145.25)	10.39 (10.22, 10.54)	0.65 (0.54, 0.76)	0.54 (0.53, 0.55)
52-week treatment	120.76 (106.14, 145.04)	10.14 (9.98, 10.29)	0.62 (0.53, 0.79)	0.58 (0.57, 0.59)
<b>Female</b>				
No treatment (0-week treatment)	64.75 (52.35, 78.86)	24.17 (23.97, 24.34)	1.00	1.00
12-week treatment	52.30 (43.09, 62.27)	16.61 (16.39, 16.67)	0.78 (0.59, 1.13)	0.69 (0.68, 0.69)
36-week treatment	42.50 (33.70, 51.29)	13.72 (13.59, 13.87)	0.64 (0.48, 0.89)	0.57 (0.56, 0.57)
52-week treatment	41.89 (33.07, 52.46)	13.38 (13.22, 13.50)	0.65 (0.48, 0.86)	0.55 (0.55, 0.56)

a. 95% CI: 95% credible interval.

**Table 3.4** 1-year Risk of Suicide and Suicide Attempt for Different Duration of Antidepressant Treatment by Age

Duration of Treatment	Suicide Rate (per 100,000) (95% CI <sup>a</sup> )	Suicide Attempt Risk (%) (95% CI)	Suicide Rate Ratio (95% CI)	Suicide Attempt Risk Ratio (95% CI)
<b>10-12 Years Old</b>				
No treatment (0-week treatment)	35.86 (23.54, 52.00)	14.96 (14.71, 15.15)	1.00	1.00
12-week treatment	28.63 (17.02, 42.97)	9.46 (9.27, 9.67)	0.80 (0.40, 1.39)	0.63 (0.62, 0.65)
36-week treatment	23.51 (13.05, 36.46)	7.91 (7.78, 8.12)	0.69 (0.35, 1.00)	0.53 (0.52, 0.54)
52-week treatment	23.53 (15.62, 36.68)	7.77 (7.56, 7.95)	0.64 (0.26, 1.22)	0.52 (0.51, 0.54)
<b>13-18 Years Old</b>				
No treatment (0-week treatment)	142.73 (123.09, 159.06)	23.34 (23.17, 23.52)	1.00 (reference)	1.00 (reference)
12-week treatment	110.99 (97.12, 129.23)	15.95 (15.80, 16.06)	0.78 (0.67, 0.94)	0.69 (0.68, 0.69)
36-week treatment	92.62 (78.80, 105.21)	13.21 (13.08, 13.32)	0.64 (0.55, 0.77)	0.57 (0.56, 0.57)
52-week treatment	90.64 (78.85, 104.19)	12.87 (12.76, 13.00)	0.63 (0.55, 0.77)	0.55 (0.55, 0.56)

a. 95% CI: 95% credible interval.

### *Sensitivity Analysis*

Table 3.5 shows how the suicide rate ratios comparing 52-week treatment with no treatment changed under different combinations of the prevalence of the discrepant. Results in the sensitivity analysis are generally consistent with those in the primary analysis, given that all the differences between estimates in the sensitivity analyses and that in the main analysis was quite limited. This suggests that the model estimates are robust to the potential unmeasured confounders caused by parameterizing the model using multiple data sources.

**Table 3.5** Sensitivity Analysis to Evaluate Bias from Parameterizing the Model with Multiple Sources<sup>a</sup>

Response Rate in the Discrepant Subgroup (High) <sup>b</sup>					
Probability of Suicide in the Discrepant Subgroup <sup>c</sup>					
Prevalence of the Discrepant Subgroup	0.25	0.50	1.00	2.00	4.00
85%	0.67 (0.29, 1.57)	0.67 (0.49, 1.00)	0.66 (0.54, 0.92)	0.67 (0.60, 0.82)	0.68 (0.62, 0.80)
55%	0.63 (0.43, 0.97)	0.59 (0.48, 0.87)	0.67 (0.54, 0.86)	0.64 (0.52, 0.87)	0.69 (0.60, 0.84)
25%	0.58 (0.44, 0.86)	0.73 (0.48, 1.00)	0.71 (0.57, 0.89)	0.71 (0.48, 0.85)	0.71 (0.55, 0.88)
Response Rate in the Discrepant Subgroup (Low) <sup>b</sup>					
Probability of Suicide in the Discrepant Subgroup <sup>c</sup>					
Prevalence of the Discrepant Subgroup	0.25	0.50	1.00	2.00	4.00
85%	0.58 (0.33, 1.07)	0.55 (0.44, 0.83)	0.59 (0.46, 0.85)	0.59 (0.42, 0.77)	0.61 (0.52, 0.67)
55%	0.55 (0.39, 0.78)	0.58 (0.32, 0.89)	0.60 (0.46, 0.83)	0.60 (0.40, 0.81)	0.61 (0.49, 0.78)
25%	0.61 (0.46, 0.76)	0.65 (0.52, 1.11)	0.63 (0.46, 0.93)	0.65 (0.45, 0.82)	0.67 (0.49, 0.79)

- Model simulation in sensitivity analysis was run for a sample of 60000 agents and repeated for 10 times.
- Response rate in the discrepant group was higher (80%) or lower (20%) compared with that in the main analysis (60%).
- Agents in the discrepant subgroup were assumed to have probability of committed suicide that was 0.25, 0.5, 1, 2 and 4 times that in the main analysis.

### 3.5 Discussion

Our study developed a carefully-calibrated microsimulation model incorporating evidence from multiple sources to examine the impact of undertreatment of depression on suicide risk in children and adolescents with MDD. We found that the 1-year suicide rate among children and adolescents with MDD was 122 per 100,000 population if they received no treatment at all, which is almost 25 times the empirically observed suicide rate in overall population of ages 10 to 17.<sup>5</sup> Compared with receiving no treatment, the suicide rate and risk of suicide attempt among children and adolescents with MDD could be reduced by 20-30% if individuals complete the acute-phase treatment, and by 30-40% with completion of both acute-phase and continuation-phase treatment. Given the fact that undertreatment is quite common among children and adolescents with MDD due to drop-out from treatment and poor retention in care,<sup>2,100,101</sup> our findings suggest there is still great potential to prevent suicide by promoting depression treatment adequacy in this population.

The estimates of the present study likely approximate the number of suicide cases that can be prevented by managing MDD as one of the risk factors for suicide. Such protective effect is supported by ecological studies showing that increasing utilization of antidepressants was associated with decrease in suicide rates.<sup>102,103</sup> However, since our study focused on children and adolescents with MDD on a one-year time horizon, the findings do not necessarily indicate the long-term effect of depression treatment in the overall youth population. To further study the impact of reducing depression undertreatment as a way to prevent suicide among children and adolescents, a simulation

model that extends to the whole child and adolescent population and involves dynamics of disease onset and healthcare seeking behaviors is needed.

The findings of the present study can help researchers obtain a better understanding of the impact of health determinants and generate plausible hypotheses for future research using real-world data. Our study is a preliminary exploration of the impact of the adequacy of depression treatment on suicide risk. A deeper understanding on dynamics of patients' depression care-seeking behavior and suicidal outcomes at the population level should be a direction for the future studies. Agent-based modeling, which shares similar features with microsimulation, has the advantage of allowing one to account for agent-agent and agent-environment interactions.<sup>17,18</sup> By applying agent-based model, the impact of different population-level interventions on suicide prevention can be assessed and compared to inform decision-making and policy or program planning.<sup>20,104,105</sup>

The findings of our study should be interpreted with caution. First, although the effect estimated from the microsimulation models can be considered a comparison between counterfactual states, causal inference can be made from a microsimulation model only when all potential determinations are considered.<sup>19</sup> Our model did not exhaust all factors related to suicide. Such factors include influence of social media, social isolation, and environmental stress.<sup>13,106</sup> For example, stressful life events (e.g., childhood maltreatment), which are considered strong risk factors for suicide,<sup>107-109</sup> have also been associated with elevated risk of persistent depressive symptoms and lack of response to the treatment.<sup>110-112</sup> Second, we did not account for interactions, including that between agents and healthcare providers and communities. The Network Episode

Model has illustrated that the pattern of mental health service use constantly changes with individuals' interactions with their social networks (e.g., families, communities, healthcare providers), and this ultimately can affect health outcomes.<sup>78,81</sup> This suggests that, even with constant baseline sociodemographic and clinical characteristics, individuals could still behave differently throughout the disease course due to interactions with their health care providers and other social networks, and this may further affect the suicidal outcomes. Third, synthesizing evidence from multiple data sources has a price, which is the bias from unmeasured determinants that distribute unevenly across different sources.<sup>87</sup> We attempted to assess the impact of this by calibrating our population-level model with efficacy evidence from clinical trials (i.e., response rate) and found that the model estimates were robust.

### **3.6 Conclusion**

The results from the microsimulation model show longer duration of antidepressant treatment can reduce suicidal behaviors among children and adolescents with MDD. At least 36-weeks of treatment can maximize suicide risk reduction. Microsimulation, which combines information from different data sources, enabled us to address questions that are challenging, if not impossible, to answer with a single dataset.

## 4 Aim 2: Development of an ABM that Simulates the Dynamics of Depression Care Seeking Behaviors in Children and Adolescents

### 4.1 Abstract

**Background:** Given the significant relationship between increased duration of antidepressant treatment on decreasing suicide rate and risk of suicide demonstrated in Aim 1, reducing undertreatment of depression is hypothesized to be effective in reducing suicidal behaviors in children and adolescents.

**Objective:** To develop an ABM that simulates the dynamics of disease course of depression and the healthcare seeking behaviors in a population of children and adolescents.

**Methods:** An ABM that consists the following sub-models was created: 1) developing depression; 2) initiating depression treatment; 3) discontinuing depression treatment; 4) changing depressive symptom; 5) achieving remission or recovery of depression; 6) developing other psychiatric disorders; 7) having medical care visits; 8) having suicidal ideation; 9) having suicide attempt; 10) having completed suicide; 11) dying of other non-suicide causes; 12) removing individuals; 13) re-creating individuals. The ABM was informed with MEPS (2016-2018), NCSAS, published clinical trial studies (i.e., TADS and TORDIA studies), CDC Fatal Injury Report, US Census Bureau, and other published literature.

**Results:** The main model-estimated results are as below: 1) prevalence of depression (including untreated and treated depression): 19.5% (95% credible interval (CI): 16.6%, 22.6%); 2) prevalence of treated depression: 4.0% (3.5%, 4.4%); 3) proportion of

individuals completing acute-phase treatment: 48.8% (95%CI: 40.1%, 56.2%); 4) suicide rate (per 100,000): 6.7 (95%CI: 4.8, 10.0); 5) risk of suicide attempt: 13.9% (95%CI: 13.5%, 14.3%).

**Conclusion:** The developed ABM simulates the process of depression development and treatment for depression among children and adolescents. This model can be used to estimate the population-level impact of suicide prevention interventions.

#### 4.1 Introduction

The findings from Aim 1 demonstrate a significant relationship between increased duration of antidepressant treatment on decreasing suicide rate and risk of suicide attempt among children and adolescents diagnosed with MDD. It is thus reasonable to hypothesize that interventions focusing on reducing undertreatment of depression (i.e., increasing those who initiate treatment or complete longer duration of antidepressant treatment) may be effective to prevent suicide in the child and adolescent population. Dynamic simulation provides an approach to evaluate hypothetical interventions in a synthetic population. We thus developed an ABM that simulated the dynamics of disease course of depression and the healthcare seeking behaviors in a population of children and adolescents to allow one to evaluate the potential effects of different interventions to prevent suicide.

The ABM developed in this Aim is based on the NEM that illustrates individuals' mental health service use and compliance to treatment throughout course of illness as a dynamic process that is influenced by multiple factors.<sup>81</sup> In the developed ABM, individuals' decision to seek depression care and continue the treatment are influenced by

their sociodemographic and clinical characteristics in a time-varying manner, and therefore, undertreatment of depression emerges as an outcome of individuals' care seeking behaviors.

This chapter introduces the overall design of the model and described the model process, parameterization and calibration.

## **4.2 Methods**

### **4.2.1 Model Overview**

An ABM to simulate the development of depression and dynamic care-seeking behaviors of children and adolescents was constructed where each time step of the model represented one month. In a simulation run, individuals with depression will initiate, continue or discontinue treatment for depression during the course of depression. The model parameters were derived from the following key data sources: MEPS (2016-2018), NCSAS (2000-2004), published landmark clinical trials (i.e., TADS and TORDIA studies), United States Census data (2016) and the CDC Fatal Injury Report (2016-2018). For parameters that could not be derived from the listed data sources, we extrapolated them from published literature. Appendix Section 8.4 lists the data sources for each parameter used in the ABM.

### **4.2.2 Attributes and Behaviors of Individuals**

The model contains two types of agents: (1) individuals (10 -18 years old) and (2) depression care providers. Sociodemographic and family characteristics, including age, sex, race/ethnicity, household income, single/no-parent household, parental suicide/suicide attempt, and parents' mental health conditions (i.e., depression, anxiety,

alcohol or drug abuse), were assigned to represent their distributions in the United States population (Appendix Section 8.5). In each time step, individuals age one month (0.083 years), and are assigned a probability of developing psychiatric disorders (i.e., depression, bipolar disorder, anxiety, ADHD, conduct disorder and alcohol/drug abuse), initiating treatment for depression (i.e., only for those with depression), discontinuing treatment for depression (i.e., only for those already on depression care) and having medical care visits (i.e., outpatient, emergency and inpatient settings) in addition to treatment for depression. In each time step, individuals may have suicidal behaviors (i.e., suicidal ideation, suicide attempt or completed suicide) or may die of non-suicide causes.

Depression care providers include primary and mental health specialty care providers. Individuals receive treatment for depression from depression care providers. Primary care providers transfer individuals that do not respond to the treatment to a specialty care provider.

#### **4.2.3 Model Process**

In each time-step (one month), the following sub-models are executed to update the characteristics of individuals:

1. Developing depression. In this sub-model, nondepressed individuals have a probability of developing depression and being characterized as depressed individuals. Among depressed individuals, the following steps are applied:
2. Initiating treatment for depression. In this sub-model, depressed individuals not on treatment for depression have a probability of initiating treatment for depression. This sub-model is not executed for non-depressed individuals.

3. Discontinuing treatment for depression. If an individual is already on treatment for depression, he/she has a probability of discontinuing (i.e., drop-out) the current treatment for depression. This sub-model is not executed for non-depressed individuals.
4. Changing depressive symptoms. In this sub-model, CDRS-R scores of depressed individuals change (i.e., worsened or improved). This sub-model is not executed for non-depressed individuals.
5. Achieving remission or recovery. Depressed individuals may remit or recover from depression according to the following rules:
  - a. If the CDRS-R score of an individual falls below 28, the individual is considered in remission.
  - b. If an individual has maintained remission for two consecutive months, the individual recovers and becomes a nondepressed individual.

This sub-model is not executed for non-depressed individuals.

6. Developing other psychiatric disorders. Both non-depressed and depressed individuals have a probability of developing other non-depression psychiatric disorders. These psychiatric disorders are considered chronic. Therefore, once individuals develop one of these psychiatric disorders, the disorder(s) will persist until leaving the cohort.
7. Having medical care visits. Both non-depressed and depressed individuals have a probability of seeking medical care in addition to treatment for depression.
8. Having suicidal ideation. Both non-depressed and depressed individuals have a probability of experiencing suicidal ideation.

9. Having suicide attempt. Both non-depressed and depressed individuals have a probability of attempting suicide.
10. Completed suicide. Both non-depressed and depressed individuals have a probability of completed suicide.
11. Dying of other causes. Both non-depressed and depressed individuals have a probability of experiencing a non-suicide-related death.
12. Removing individuals who die or reach age 18 (in non-depressed and depressed individuals).
13. Re-creation of a nondepressed individual for each of the individuals removed.

#### 4.2.4 Model Parameterization

Equations to calculate the probabilities for each of the sub-models above were determined using the best available data sources.

##### 4.2.4.1 Developing Depression

The following equations were used to estimate the probability of developing depression (i.e., the probability that nondepressed individuals develop depression in a time step):

$$\begin{aligned} \text{logit}(\mu_{(depression=1,1\text{ year})}) = & \beta_{d0} + \beta_{d1}age + \beta_{d2}male + \beta_{d3}nhw + \beta_{d4}nhb + \\ & \beta_{d5}hisp + \beta_{d6}lowIncome + \beta_{d7}midIncome + \beta_{d8}singleParent + \\ & \beta_{d9}fathermental + \beta_{d10}mothermental + \beta_{d11}bipolar + \beta_{d12}ADHD + \\ & \beta_{d13}cdodd + \beta_{d14}anxiety + \beta_{d15}adAbuse \end{aligned}$$

(1)

$$\mu(\text{depression}=1,1 \text{ year}) = \frac{e^{\text{logit}(\mu(\text{depression}=1,1 \text{ year}))}}{e^{\text{logit}(\mu(\text{depression}=1,1 \text{ year}))} + 1}$$

(2)

$$P_{(\text{depression}=1, \text{one time step})} = 1 - e^{\left(\frac{-\mu(\text{depression}=1,1 \text{ year})}{12}\right)}$$

(3)

In Equation (1),

*age* is a continuous variable of the individuals' age in the current time-step

*Sex*:

*male* is binary male = 1, female = 0

*Race/Ethnicity*:

*hisp* for Hispanic is binary: hisp = 1, nhb = 0, nhw = 0

*nhb* for non-Hispanic Black is binary: hisp = 0, nhb = 1, nhw = 0

*nhw* for non-Hispanic White is binary: hisp = 0, nhb = 0, nhw = 1

Other race/ethnicity: hisp = 0, nhb = 0, nhw = 0)

*Household Income*: two dummy variables were created to represent the three-level (i.e., low, middle and high) household income:

*lowIncome* is binary: lowIncome = 1, midIncome = 0

*middle income* is binary: lowIncome = 0, midIncome = 1

high income is represented as lowIncome = 0, midIncome = 0

*Single Parent Household*:

*singleParent* = 1 if the individual is in a single/no parent home, else

*singleParent* = 0.

*Parent Mental Health Conditions ever*:

$fathermental = 1$  if the individual's father has any mental conditions, else  $fathermental = 0$ .

$mothermental = 1$  if the individual's mother has any mental conditions, else  $mothermental = 0$ .

*Agent Mental Health Conditions:*

$bipolar = 1$  if the individual has bipolar disorder, else  $biplar = 0$ .

$Adhd = 1$  if the individual has ADHD, else  $adhd = 0$ .

$Cdodd = 1$  if the individual has conduct and/or oppositional defiant disorder, else  $cdodd = 0$ .

$Anxiety = 1$  if the individual has anxiety disorder, else  $anxiety = 0$ .

$adAbuse = 1$  if the individual has alcohol or drug abuse, else  $adAbuse = 0$ .

In Equation (1),  $\text{logit}(\mu_{(depression=,1\text{ year})})$  is an estimate of the likelihood of depression over 12 months. Equation (2) calculates the depression rate during 12 months, assuming 12-month follow-up for all subjects in the sample. The probability of developing depression at one time step was thus calculated with Equation (3), where  $\mu_{(depression=,1\text{ year})}/12$  converts the yearly rate of depression to a monthly rate.

Equation (1) was estimated using the NCSAS data. The rationale for choosing NCSAS over other possible data sources, such as MEPS, is that the NCSAS includes both treated and untreated (i.e., never received any treatment) depressed individuals, which provides more comprehensive information from which to estimate the probability of developing depression than MEPS, which only provides an estimate of those who had some medical visits or prescriptions related to the reported condition. The MEPS questions to capture depression status (i.e., Patient Health Questionnaire-2(PHQ-2)) are

not administered to children, only adults. Therefore, depression status for untreated is not available in the MEPS data.

#### 4.2.4.2 Treatment for depression

##### Initiating Treatment for Depression

Depressed individuals who are not on treatment for depression have a probability of initiating treatment for depression. The probability of initiating treatment for depression was calculated using the following equations:

$$\begin{aligned} \text{logit}(\mu_{(treatment=,1\ year)}) &= \beta_{t0} + \beta_{t1}age + \beta_{t2}male + \beta_{t3}nhw + \beta_{t4}nhb + \\ &\beta_{t5}hisp + \beta_{t6}lowIncome + \beta_{t7}midIncome + \beta_{t8}singleParent + \\ &\beta_{t9}fathermental + \beta_{t10}mothermental + \beta_{d11}mental \end{aligned} \quad (4)$$

$$\mu_{(treatment=,1\ year)} = \frac{e^{\text{logit}(\mu_{(treatment=,1\ year)})}}{e^{\text{logit}(\mu_{(treatment=,1\ year)})} + 1}$$

(5)

$$P_{(treatment=,one\ time\ step)} = 1 - e^{\left(-\frac{\mu_{(treatment=,1\ year)}}{12}\right)}$$

(6)

In this study, the probability of initiating treatment for depression after developing depression was approximated as the probability of initiating treatment for a mental condition after developing the mental conditions. This is based on the assumption that an individual can initiate treatment for depression when seeking care for other psychiatric disorders. Equation (4) estimates the logit of initiating treatment for depression. In Equation (4), “mental” is a composite variable to indicate if an individual has any other

mental health conditions (i.e., depression, bipolar disorder, anxiety, ADHD, conduct disorder and alcohol/drug abuse).

Equation (4) was estimated using the NCSAS data. The NCSAS data include individuals who were treated and never treated, which enables one to estimate the probability for one to initiate treatment when developing mental conditions (i.e., the probability that an untreated individual initiates treatment). A depressed individual was defined as treated depression once he/she initiates treatment for depression for the first time. Depressed individuals that never initiated treatment for depression were defined as untreated.

#### Discontinuing Treatment for Depression

Depressed individuals receiving treatment for depression have a probability of discontinuing the current treatment in a time-step. The probability of discontinuing treatment for depression was calculated based on the following equations:

$$\text{logit}(\mu_{(drop=,1\text{ year})}) = \beta_{drop0} + \beta_{drop1}adAbuse + \beta_{drop2}ADHD + \beta_{drop3}severeDepression$$

(7)

$$\mu_{(drop=,1\text{ year})} = \frac{e^{\text{logit}(\mu_{(drop=1,1\text{ year})})}}{e^{\text{logit}(\mu_{(drop=,1\text{ year})})} + 1}$$

(8)

$$P_{(drop=1,one\text{ time step})} = 1 - e^{\left(-\frac{\mu_{(drop=1,1\text{ year})}}{12}\right)}$$

(9)

In Equation (7), “severeDepression” represents severity of depressive symptoms (severe depression = 1, mild to moderate depression = 0).

Since there is no available data source to directly estimate the association between treatment discontinuation and an individual’s characteristics,  $\beta$ s in Equation (7) were derived from a published meta-analysis study that evaluated factors associated with medication adherence among children and adolescents with mental health conditions.<sup>113</sup> The study found significant impact of alcohol/drug abuse, ADHD and depression severity on treatment nonadherence. The coefficients in Equation (7) were extrapolated by converting (i.e., taking natural log of) the reported ORs in the study into the coefficients used in the equation. The intercept in Equation (7) was assumed 0 at the beginning and determined in the calibration process. The final equations used in ABM are listed in Appendix Section 8.5.

#### ***4.2.4.3 Depressive Symptoms Change***

CDRS-R scores measure the severity of depressive symptoms. Depressive symptom severity was categorized based on established CDRS-R score cut-off points used in published clinical trials,<sup>94,114</sup> where 35-60 defined mild to moderate depression and above 60 defined severe depression.

CDRS-R scores were assumed to change as a linear function of natural log of days since depression onset. The following equations were applied to update the CDRS-R score at each time step:

$$CDRS - R Score_{i1} = Baseline CDRS - R Score_i + \beta_{sij} \ln(j * 30) + \varepsilon_{ij}$$

where  $j = 1$  (10)

$$CDRS - R Score_{ij} = CDRS - R Score_{i, j-1} + \beta_{s_{ij}} \ln\left(\frac{j}{j-1}\right) + \varepsilon_{ij} \quad \text{where } j \geq 2$$

(11)

In Equations (10) and (11), *i* and *j* represent an individual *i* at the *j*<sup>th</sup> month since depression onset. Equation (10) was used to calculate the CDRS-R score change from baseline to the end of the first month after depression onset. Equation (11) was used to update the CDRS-R scores since the second month after depression onset.  $\beta_{s_{ij}}$  is the change of the CDRS-R score with every month. The  $\beta$ s correspond to the treatment for depression status (i.e., on treatment or not) in the current time step. The random error,  $\varepsilon_{ij}$ , follows a normal distribution  $N(0, 0.1)$ . Variability in individual trajectories of depressive symptom change was accounted for by assuming  $\beta$ s among depressed individuals were distributed with a certain mean (i.e., fixed effect) and variance (i.e., random effect).

The process for determining the mean and variance of  $\beta$ s was described in Aim 1. The fixed and random effects of  $\beta$ s are listed in Appendix Section 8.5.

#### 4.2.4.4 *Other Psychiatric Disorders*

Nondepressed and depressed individuals can develop other psychiatric disorders, and the probabilities of developing a psychiatric disorder (excluding depression) were calculated with the following equations:

$$\text{logit}(\mu_{(comorbid_k=1,1 \text{ year}, \text{ depression status})}) = \beta_{c_k h_0} + \beta_{c_k h_1} \text{child} + \beta_{c_k h_2} \text{male} + \beta_{c_k h_3} \text{nhw} + \beta_{c_k h_4} \text{nhb} + \beta_{c_k h_5} \text{hisp} + \beta_{c_k h_6} \text{lowIncome} +$$

$$\beta_{c_k h 7} midIncome + \beta_{c_k h 8} singleParent + \beta_{c_k h 9} fathermental + \beta_{c_k h 10} mothermental \quad (12)$$

$$\mu_{(comorbid_k=1, 1 \text{ yea}, \text{ by depression status})} = \frac{e^{\text{logit}(\mu_{(comorbid_k=1 \text{ over } 12 \text{ month}, \text{ depression status})})}}{e^{\text{logit}(\mu_{(comorbid_k=1 \text{ over } 12 \text{ mont}, \text{ depression status})})} + 1} \quad (13)$$

$$P_{(comorbid_k=1, \text{one time step})} = 1 - e^{\left(-\frac{\mu_{(comorbid_k=1, 1 \text{ year}, \text{ depression status})}}{12}\right)} \quad (14)$$

Where,  $k$  represents each psychiatric disorder (1=bipolar disorder, 2=ADHD, 3=CD/ODD, 4=anxiety, 5=alcohol/drug abuse), and  $h$  represents depression status (1=depressed, 0=non-depressed). A non-depressed individual that developed bipolar disorder was characterized as a depressed individual.

Coefficients in Equations (12) for bipolar disorders, ADHD, conduct disorders, and anxiety disorders were estimated directly from MEPS 2016-2018, respectively, to obtain the most up-to-date information. Since the MEPS data do not report alcohol/drug abuse, we referred to NCSAS to estimate the coefficients for this disorder. The parameterized equations used in the ABM are listed in Appendix Section 8.5.

#### 4.2.4.5 Medical Care Visits

Medical care visits include any outpatient (including hospital outpatient department, clinics and other office-based visits), emergency department and inpatient visits individuals have in addition to treatment for depression. The purpose of including this sub-model is to estimate medical visits in the population. All individuals, including

depressed and non-depressed, have a probability of medical care visits in a time step. The probability of having a medical care visit(s) was calculated using the following equations:

$$\log\left(\frac{\mu(\text{Visit}_{kh}=1, \text{depression status})}{1 \text{ year}}\right) = \beta_{v_k h 0} + \beta_{v_k h 1} \text{age} + \beta_{v_k h 2} \text{male} + \beta_{v_k h 3} \text{nhw} + \beta_{v_k h 4} \text{nhb} + \beta_{v_k h 5} \text{hisp} + \beta_{v_k h 6} \text{lowIncome} + \beta_{v_k h 7} \text{midIncome}$$

(15)

$$\mu(\text{Visit}_{kh}=1, 1 \text{ year}) = e^{\log\left(\frac{\mu(\text{Visit}_{kh}=1, \text{depression status})}{1 \text{ year}}\right)}$$

(16)

$$P(\text{Visit}_k=1, \text{one time step}) = 1 - e^{\left(\frac{\mu(\text{Visit}_{kh}=1, \text{depression status}, 1 \text{ year})}{12}\right)}$$

(17)

Equation (15) is a Poisson regression model that was used to estimate the rate of medical care visits in a year  $\mu(\text{Visit}_{kh}=1)$ , and Equation (17) estimates the probability of having a medical care visit in a time step.

In the equations above, k represents the type of medical care visits (1=outpatient, 2=emergency, 3=inpatient), and h represents depression status (1 = treated depression, 0 = untreated depression or nondepressed). Coefficients for Equation (15) were directly estimated based on the MEPS data. The parameterized equations used in the ABM are listed in Appendix Section 8.5.

#### **4.2.4.7 Suicidal Events**

Suicidal events include suicidal ideation, suicide attempt and completed suicide. Different approaches were applied to estimate the probability of suicidal ideation, suicide

attempt, and completed suicide, to account for the difference among these suicidal behaviors.

The equation used to calculate the probability of having suicide ideation was discussed earlier in the Aim 1 microsimulation model.

In the ABM, the probabilities of suicide attempt and completed suicide were recalculated at each time step based on suicidal ideation status (i.e., having suicidal ideation or not) and depression status. The process for determining the probability of suicide attempt and completed suicide was described in Aim 1. Probabilities of suicide attempt and completed suicide are listed in Appendix Section 8.5.

#### ***4.2.4.6 Death and Re-creation of Individuals***

The synthetic population is an open population where individuals leave because of death or age (over 18 years old) and new individuals enter.

In addition to death caused by suicide, individuals may die of non-suicidal causes in each time step. Probability of dying at one time step was extrapolated from the United States census data according to age groups  $<15$  and  $\geq 15$  years old (Appendix Section 8.5).

To maintain a constant number of individuals in the synthetic population, a new individual aged 10 years old is re-created (i.e., enters the cohort) with every individual that died or leaves the cohort at age 18 years old.

#### **4.2.5 Model Calibration**

Calibration was conducted for the parameters that cannot be estimated directly from available data source.

There was no data to directly estimate the probability of discontinuing treatment for depression among the depressed individuals. Therefore, coefficients in Equation (7), based on which the probability of discontinuing treatment for depression was calculated, were extrapolated from published literature assuming an intercept of 0 before calibration. The intercept of Equation (7) was then adjusted until the 95% CI (calculated based on 20 simulation runs) of the model-estimated proportion of individuals that completed the first 12 weeks of treatment (i.e., acute-phase treatment) included the empirically observed value.<sup>2</sup>

Although studies have shown that severe depression is more likely associated with risk of suicidal behaviors,<sup>115</sup> no information is available to quantify the association between depression severity and the probability of completed suicide. We assumed that there was a certain cut-off point in the CDRS-R score, above which resulted in increased probability of completed suicide and suicide attempt for the depressed individuals compared with that in the non-depressed individuals. Therefore, different cut-off points from 60 to 90 were tested until the 95% credible interval (calculated based on 20 simulation runs) of the model-estimated suicide rate included the suicide rate obtained from CDC Fatal Injury Report (2016-2018). The final cut-off point to use in the model was 80.

### **4.3 Model Estimates**

The main model estimates include prevalence of depression (including untreated and treated depression), prevalence of treated depression, proportion of individuals that completed acute-phase treatment, suicide rate and risk of suicide attempt in the population (Table 4.1).

**Table 4.1** Main Estimates of the Agent-Based Model

	Model-Estimated Results (95% CI) <sup>a</sup>
Prevalence of Depression (%)	19.5 (16.6, 22.6)
Prevalence of Treated Depression (%)	4.0 (3.5, 4.4)
Proportion of Individuals Completing Acute-phase Treatment (%)	48.8 (40.1, 56.2)
Suicide Rate (per 100,000)	6.7 (4.8, 10.0)
Risk of Suicide Attempt (%)	13.9 (13.5, 14.3)

a. 95%CI: 95% credible intervals

#### 4.4 Summary

In this aim, an ABM was developed to simulate the process of depression development and treatment for depression among children and adolescents. Suicide and suicide attempts can occur at any time during the process. Because the model synthesized a population that included the overall population (including the depressed and nondepressed individuals), this ABM thus can be used to evaluate the population-level impact of suicide prevention interventions. Undertreatment of depression (i.e., no treatment and attrition from treatment before remission is achieved) emerges from the ABM process, which allows one to examine how the interventions that reduce undertreatment of depression influence the suicidal outcomes in the population.

## **5 Aim 3: Impact of Different Interventions on Preventing Suicide and Suicide Attempt Among Children and Adolescents: An Agent-Based Model Simulation**

### **5.1 Abstract**

**Background:** Despite great efforts invested in suicide prevention since 2001, evidence for the effects of the suicide prevention interventions in children and adolescents is quite limited.

**Objective:** To estimate the potential population impact of different interventions in preventing suicidal behaviors in children and adolescents.

**Methods:** An ABM informed by national survey data and clinical trials simulated the dynamic process of depression development and care-seeking behaviors among children and adolescents aged 10-18. Four interventions were considered: Intervention 1: depression screening (reducing untreated depression by 20%, 50%, 80%); Intervention 2: reducing attrition during treatment for depression (increasing proportion of acute-phase treatment completion to 90%); Intervention 3: suicide intervention (screened and treat those in need of suicide care) for the depressed individuals; Intervention 4: universal suicide intervention (intervening 20%, 50% and 80% of individuals) in medical settings. Interventions were examined both separately and combined (Intervention 1+2, 1+3, and 2+3). Suicide rate and risk of suicide attempt were estimated for each scenario of each intervention and compared with baseline.

**Results:** No significant reduction of suicide rate was observed for any of the interventions. Intervention 1 showed moderate effect on reducing risk of suicide attempt. Neither Intervention 2 nor 3 alone showed significant effect on reducing the risk of

suicide attempt. Significant decrease in the risk of suicide attempt was observed for Intervention 4 (intervened individuals: 20%: -0.68% (95% CI: -0.87%, -0.55%), 50%: -1.47% (95% CI: -1.61%, -1.77%), 80%: -2.89% (95% CI: -4.57%, -2.31%). Intervention 1 + 2 and Intervention 1 + 3 revealed larger decrease in risk of suicide attempt compared with implementing each intervention alone (1+2: reduction of untreated depression: 20%: -0.33% (95% CI: -0.92%, 0.04%); 50%: -0.56% (95% CI: -1.06%, -0.17%); 80%: -0.78% (95% CI: -1.29%, -0.40%); 1+3: 20%: -0.27% (95% CI: -0.52%, -0.16%); 50%: -0.66% (95% CI: -0.90%, -0.46%); 80%: -0.90% (95% CI: -1.10%, -0.69%)).

**Conclusion:** Universal suicide intervention in medical care settings may be more effective in reducing suicidal behaviors in the population compared with interventions that reduce undertreatment of depression.

## 5.2 Introduction

Despite great efforts invested in suicide prevention since 2001,<sup>46</sup> suicide rate among children and adolescents still increased significantly by over 80% during 2007-2017, and accounted for more than 33% of deaths in this age group.<sup>5,27</sup> According to the most recent vital statistics surveillance report by CDC, suicide rate in the younger population aged 10-25 increased in 2020 in the context of declines of overall suicide rate in the older age groups.<sup>116</sup> A sharp rise in the studies about suicide prevention has been seen since 2005,<sup>117</sup> but evidence for the effects of the suicide prevention strategies on children and adolescents is quite limited compared with that in adults.

An important strategy to reduce suicidal behaviors (i.e., completed suicide, suicide attempt and suicidal ideation) is to treat underlying mental health conditions associated with high risk of self-harm and suicide attempts. Depression is one of the strongest risk factors for suicide, and the efficacy of pharmacological (e.g., antidepressants) and non-pharmacological (e.g., CBT) treatment in reducing suicidal ideation has been proved in several clinical trials.<sup>69,90</sup> However, in the U.S., 60% of children and adolescents diagnosed with depression do not receive any treatment or professional counseling services,<sup>28</sup> and more than half discontinue treatment for depression within the first 3 months in spite of a recommended treatment duration for at least 36 weeks.<sup>2,82</sup> Population-level evidence supporting the effectiveness of reducing undertreatment of depression on preventing suicide is limited. The findings from Aim 1 suggest a significant association between increased duration of antidepressant treatment and decreased risk of suicidal behaviors among children and adolescents with depression. It is thus reasonable to theorize that interventions which reduce undertreatment of

depression (i.e., shorter duration of depression treatment compared with recommendation and no treatment) in the population are effective in preventing suicide. However, there is limited data that includes information of implementation of these interventions in children and adolescents, and no direct evidence is available for or against the effect of such interventions in the population.<sup>118</sup>

Simulations that involve system dynamics (e.g., ABM) are increasingly utilized in public health.<sup>119,120</sup> ABM allows one to conduct experiments on synthetic populations when empirical data on actual implementation of the interventions or policies to be evaluated is not available. One can thus make a good decision for implementation based on simulated data. As a bottom-up approach in which dynamics at the macro level (e.g., population) emerge from behaviors at micro level (e.g., individuals),<sup>121</sup> population-level effects of policies and interventions can be tested using ABM while accounting for the complex behaviors and interactions of individuals in a population. The present study was conducted to evaluate if and how much interventions that decrease undertreatment of depression can reduce suicidal behaviors in children and adolescents. Using the ABM developed in Aim 2, in which undertreatment of depression (i.e., no treatment and attrition from treatment) in the population emerges from individuals' care seeking behaviors (i.e., initiating or discontinuing treatment), we were able to simulate different scenarios in which undertreatment of depression was reduced and evaluate how suicidal outcomes in the population change correspondingly.

## **5.2 Methods**

### **5.2.1 Model Settings**

We initialized 100,000 nondepressed individuals age from 10 to 18. One complete simulation includes 170 months with the first 110 months being a “burn-in” period where the model was run to achieve stabilized demographic and clinical distributions in the synthesized population. The last 60 months (5 years) were counted in the model analysis.

### **5.2.2 Undertreatment of Depression**

In this study, undertreatment of depression was defined as receiving no treatment for depression (i.e., untreated depression) or discontinuing treatment for depression before completing the first 36 weeks of treatment (i.e., both acute- and continuation-phase treatment). Definition of untreated depression was described in Aim 2. Briefly, untreated depression was defined as depressed individuals that never received any treatment since depression onset. A depressed individual that initiated treatment ever was defined as treated.

### **5.2.3 Interventions**

Four interventions were examined in this study. The interventions that reduce undertreatment of depression in the population included depression screening and reducing attrition from treatment for depression. We also tested interventions that directly focused on individuals with increased risk of suicide, including suicide intervention for the depressed individuals and universal suicide intervention in medical care settings.

#### *Baseline*

The suicide rate and risk of suicide attempt without any interventions implemented were defined as the baseline values.

### *Depression Screening (Intervention 1)*

Depression screening is an intervention to identify individuals who need depression care and have them initiate treatment. In this study, depression screening was assumed to identify and have individuals with untreated depression initiate treatment for depression. Depression screening tested in this study thus reduce the prevalence of untreated depression in the population. To manipulate different effects of depression screening, we adjusted the probability of initiating treatment for depression to achieve a 20%, 50% and 80% reduction in the prevalence of untreated depression from baseline, respectively.

### *Reducing Attrition from Treatment (Intervention 2)*

In this study, reducing attrition from treatment for depression was to reduce individuals' probability of discontinuing treatment for the depression so that the proportion of individuals that completed acute- and continuation-phase treatment would increase. We adjusted the probability of discontinuing treatment so that the model-estimated proportion of individuals who completed the first 12 weeks of treatment (i.e. acute-phase treatment) was increased to 90%, compared with 50% at baseline (Table 4.1).

### *Suicide Intervention for the Depressed (Intervention 3)*

Suicide intervention for the depressed individuals assumed to screen all depressed individuals seen by depression care providers for suicide risk and treat those at elevated risk of suicide. An individual was considered at elevated suicide risk if he/she had suicidal ideation or attempted suicide in the time-step. We assumed that all individuals at

elevated risk of suicide can be identified with suicide screening and receive treatment for suicidal behaviors. Two evidence-based treatment for suicidal ideations were included: CBT, which was applied to individuals with suicidal ideation and brief intervention and contact (BIC), which was applied to individuals with suicide attempt. The efficacy of CBT and BIC was extrapolated from published literature. Specifically, the risk of suicide attempt of those intervened with CBT was 0.47 times that of those treated as usual.<sup>122</sup> Suicide rate among those intervened with BIC dropped 10 times compared with those treated as usual.<sup>123</sup> The effect of CBT or BIC for the depressed was thus manipulated as altering the post-CBT probability of suicide attempt to 0.47 times the pre-CBT probability of suicide attempt, and the post-BIC probability of completed suicide to 0.1 times the pre-BIC probability of completed suicide.

#### *Universal Suicide Intervention (Intervention 4)*

A central strategy to prevent suicide is to apply screen all patients in medical care settings for suicide risk and treat those who need suicide care.<sup>35</sup> Instead of only intervening the depressed individuals, universal suicide intervention screened any individuals in medical settings and treated those with suicidal ideation (intervened with CBT) or having attempted suicide (intervened with BIC). We examined different scenarios with a total of 20%, 50% or 80% of individuals in medical care settings were screened, respectively. Individuals were considered in medical care settings if they had at least one medical visit in the time-step. The efficacy of CBT and BIC was applied in the same way as Intervention 3.

Each intervention was first examined separately. We also evaluated the effects of implementing following interventions together: 1) Intervention 1 + Intervention 2 refers

to implementation of depression screening and reducing attrition during treatment for depression together; 2) Intervention 1 + Intervention 3 refers to implementation of depression screening and suicide intervention for the depressed individuals together; 3) Intervention 2+ Intervention 3 refers to implementation of reducing attrition from treatment of depression and suicide intervention for the depressed individuals together.

#### **5.2.4 Suicidal Outcomes in the Population**

The suicidal outcomes in the population considered in this study include suicide rate and risk of suicide attempt. Suicide rate was calculated as the total number of suicides divided by the total population. Risk of suicide attempt was calculated as the number of individuals that attempted suicide ever (i.e., had suicide attempt at least once) divided by the total population. Suicide rates and risk of suicide attempt under each scenario of the experiments were examined. The absolute change of suicide rate and risk of suicide attempt between each of the intervened scenario and the baseline was reported.

Simulation for each intervention scenario was repeated 20 times. The median and 95% credible intervals (CIs) were reported. To estimate the CIs, the 20 estimates were ordered and the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles were taken as the lower and upper bounds of the CIs. The difference from baseline with a CI that did not include 0 was considered significant.

#### **5.2.5 Sensitivity Analysis**

##### *Impact of Model Parameters on Estimated Suicide Rate and Risk of Suicide Attempt*

A series of one-way sensitivity analyses were conducted on each of the key input model parameters (i.e., probabilities of developing depression, initiating treatment for

depression, discontinuing treatment for depression, developing other psychiatric disorders, and having suicidal ideation) to test how robust the model-estimated suicidal outcomes (i.e., suicide rate and risk of suicide attempt) were to the change of these parameters. Each parameter was tested by changing it by  $\pm 5\%$  and  $\pm 20\%$ , respectively.

The ABM was also run with different cut-off points in the CDRS-R scores (0, 40, 60) above which defined the group of depressed individuals with the increased probability of suicide attempt and completed suicide. Suicide rate and risk of suicide attempt were reported with each cut-off point in the CDRS-R scores.

#### *Sensitivity Analysis on the Cut-off Points in CDRS-R Scores*

We conducted sensitivity analyses by setting the cut-off point in CDRS-R scores to 0 (i.e., removing the cut-off point and assumed all depressed individuals had increased probability of completed suicide and suicide attempt) and evaluated how the effects of the interventions may change.

### **5.3 Results**

#### *Primary Analysis*

The baseline prevalence of depression (including treated and untreated depression) was 19.5% (95% CI: 16.6%, 26.6%) (Table 4.1), and the prevalence of treated depression was 4.0% (95% CI: 3.5%, 4.4%) (Table 4.1). The baseline suicide rate was 6.70 (95% CI: 4.80, 10.00) per 100,000, and the baseline risk of suicide attempt was 13.90% (95% CI: 13.50%, 14.32%) (Table 5.1). Suicide rate and risk of suicide attempt for different scenarios of each intervention are listed in Table 5.1.

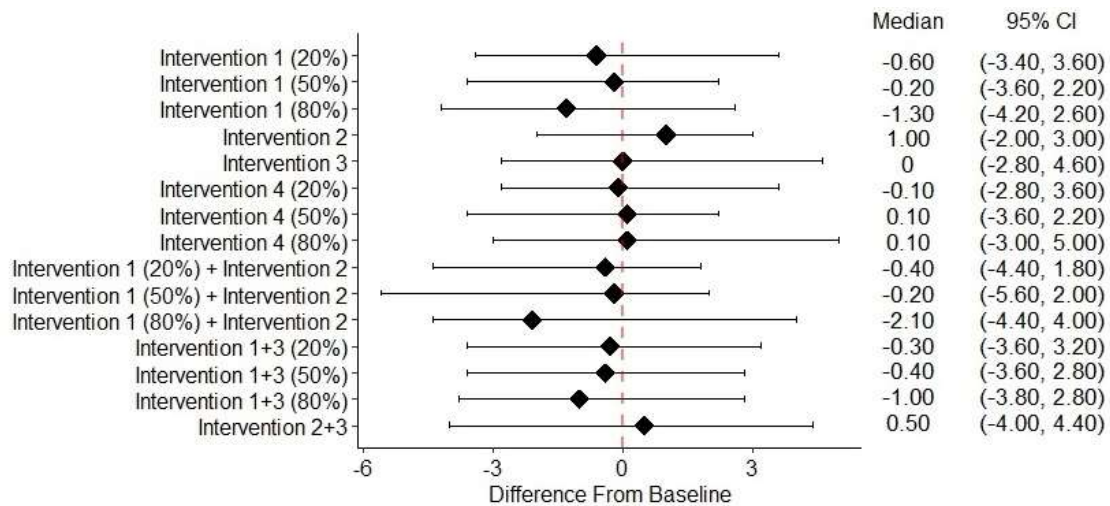
**Table 5.1** Model Simulated Suicidal Outcomes with Different Interventions

	Suicide Rate, per 100000 (95% CI <sup>a</sup> )	Risk of Suicide Attempt, % (95% CI)
Baseline	6.70 (4.80, 10.00)	13.90 (13.50, 14.32)
Depression screening		
Reduction of untreated depression		
20%	7.10 (4.60, 10.20)	13.62 (13.43, 14.05)
50%	6.20 (4.20, 9.40)	13.48 (12.86, 13.86)
80%	5.80 (3.00, 7.40)	13.25 (12.94, 13.65)
Reducing Attrition During Treatment	7.10 (6.40, 8.60)	13.83 (13.67, 13.97)
Suicide intervention on the depressed	6.70 (4.80, 9.40)	13.78 (13.66, 13.93)
Universal Suicide intervention		
Individuals screened		
20%	6.80 (3.80, 8.40)	13.14 (12.98, 13.25)
50%	6.80 (5.00, 8.80)	12.31 (12.10, 12.53)
80%	6.60 (4.80, 9.80)	11.62 (11.53, 11.75)
Depression Screening + Reducing Attrition During Treatment		
Reduction of untreated depression		
20%	6.20 (4.20, 8.40)	13.56 (13.40, 13.67)
50%	6.10 (4.40, 8.60)	13.30 (13.11, 13.43)
80%	5.50 (3.80, 8.80)	13.09 (12.90, 13.21)
Depression Screening + Suicide intervention for the depressed		
Reduction of untreated depression		
20%	6.40 (4.40, 9.00)	13.49 (13.29, 13.60)
50%	6.50 (4.60, 8.40)	13.09 (12.93, 13.25)
80%	6.00 (3.80, 7.60)	12.88 (12.73, 13.05)
Reducing Attrition During Treatment + Suicide intervention for the depressed	7.90 (5.00, 9.20)	13.68 (13.52, 13.90)

a.95% credible interval.

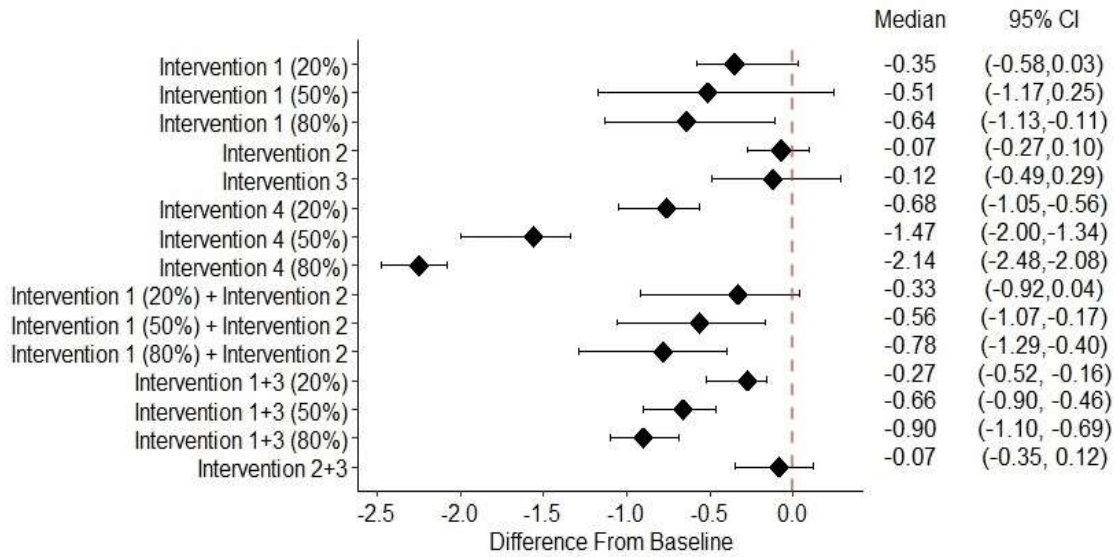
No significant effects of reducing suicide rate were found in any of the examined interventions (Figure 5.1). When implemented alone, depression screening showed significant effect on reducing risk of suicide attempt when 80% of untreated depression was reduced in the population (20% reduction: -0.35% (95% CI: -0.58%, 0.03%); 50% reduction: -0.51% (95% CI: -1.17%, 0.25%); 80% reduction: -0.64% (95% CI: -1.13%, -0.11%)). Neither reducing attrition from treatment nor suicide intervention for the depressed individuals alone showed significant effect on reducing risk of suicide attempt. With universal suicide intervention in medical care settings, the risk of suicide attempt decreased by 0.68% (95% CI: 0.55%, 0.87%), 1.47% (95% CI: 1.77%, 1.61%), and 2.89% (95% CI: 2.31%, 4.57%) if 20%, 50%, and 80% of individuals in medical settings were intervened (i.e., screened and treated if at elevated risk of suicide), respectively (Figure 5.2).

**Figure 5.1** Change of Suicide Rate from Baseline of Different Intervention Scenarios<sup>a</sup>



a. Intervention 1: depression screening; Intervention 2: promoting depression treatment completion; Intervention 3: suicide intervention for the depressed; Intervention 4: universal suicide intervention

**Figure 5.2** Change of Risk of Suicide from Baseline of Different Intervention Scenarios<sup>a</sup>



a. Intervention 1: depression screening; Intervention 2: promoting depression treatment completion; Intervention 3: suicide intervention for the depressed; Intervention 4: universal suicide intervention.

When depression screening and reducing attrition from treatment for depression were implemented together, the decrease in the risk of suicide attempt increased compared with implementation either of the interventions alone (20% reduction: -0.33% (95% CI: -0.92%, 0.04%); 50% reduction: -0.56% (95% CI: -1.06%, -0.17%); 80% reduction -0.78% (95% CI: -1.29%, -0.40%). Combining depression screening with suicide intervention for the depressed individuals also increased the effects of reducing risk of suicide attempt in the population compared with implementing either intervention alone (20% reduction: -0.27% (95% CI: -0.52%, -0.16%); 50% reduction: -0.66% (95% CI: -0.90%, -0.46%); 80% reduction: -0.90% (95% CI: -1.10%, -0.69%)). However, combining suicide intervention for the depressed individuals with reducing attrition from the treatment did not show any significant effects on the risk of suicide attempt (Figure 5.2).

### *Sensitivity Analysis*

The model-estimated suicide rate and risk of suicide attempt were generally robust to the probability of developing depression, initiating treatment for depression, discontinuing treatment for depression, and developing other psychiatric disorders. The probability of suicide ideation had larger impact on risk of suicide attempt than on suicide rate. Within 40% difference in the probability of suicidal ideation (i.e., between -20% to 20% change in the parameter), the risk of suicide attempt showed 2.16% change, but the suicide rate did not change much (Table 5.2).

The cut-off points in CDRS-R scores above which defined in the increased probability of completed suicide and suicide attempt had quite obvious impact on suicide rate and risk of suicide attempt. Compared with the cut-off point used in the primary analysis model (i.e., 80), suicide rate increased to 20.8 per 100,000, and risk of suicide attempt increased to 17.28% when cut-off point was set to 0 (Table 5.2).

The baseline suicide rate when the cut-off point in CDRS-R scores was set to 0 was 20.8 (95% CI: 19.2, 22.8) per 100,000. The risk of suicide attempt was 17.28 (95% CI: 17.25%, 17.37%) (Table 5.2). The change of the risk of suicide attempt for most intervention scenarios was slightly larger than those in the primary analysis, except for reduction of untreated depression of 20% and 50% (Appendix Section 8.6).

**Table 5.2** Sensitivity Analysis of Model-Estimated Suicide Rate and Risk of Suicide Attempt in the Population with Modified Input Model Parameters<sup>a</sup>

Cut-off	Suicide Rate				Risk of Suicide Attempt			
	0	40	60	80 <sup>c</sup>	0	40	60	80 <sup>c</sup>
Points in CDRS-R Scores <sup>b</sup>	20.80 (19.20, 22.80)	19.80 (18.20, 21.40)	13.90 (10.40, 20.20)	6.70 (4.80, 10.00)	17.28 (17.25, 17.37)	17.02 (17.01, 17.17)	15.82 (15.79, 15.96)	13.90 (13.50, 14.32)
Change from the original values								
	-20%	-5%	5%	20%	-20%	-5%	5%	20%
Prob. of suicidal ideation	8.00 (6.20, 8.40)	7.80 (4.60, 8.4)	7.80 (5.60, 9.20)	8.20 (5.20, 9.60)	12.69 (12.59, 12.9)	13.64 (13.29, 13.70)	14.17 (14.06, 14.18)	14.85 (14.79, 14.90)
Prob. of developing depression	8.00 (6.00, 8.80)	8.20 (6.40, 8.60)	7.40 (7.40, 9.60)	7.60 (6.00, 8.40)	14.13 (14.01, 14.26)	13.94 (13.88, 14.07)	13.85 (13.77, 14.02)	13.75 (13.64, 13.90)
Prob. of initiating treatment for depression	7.40 (7.20, 8.80)	7.20 (5.80, 8.20)	7.40 (7.20, 9.40)	7.20 (5.60, 7.60)	13.89 (13.77, 13.98)	13.96 (13.82, 13.99)	13.86 (13.80, 13.91)	13.91 (13.78, 13.98)
Prob. of discontinuing depression treatment	6.40 (6.40, 7.40)	6.40 (5.40, 8.40)	7.60 (6.20, 8.20)	8.20 (6.40, 9.00)	13.88 (13.82, 14.00)	13.90 (13.87, 14.06)	13.91 (13.81, 14.03)	13.94 (13.92, 14.00)
Prob. of developing other psychiatric disorders								
Anxiety	7.60 (5.00, 9.80)	6.60 (6.20, 9.60)	6.20 (5.40, 8.60)	7.00 (5.80, 8.00)	13.97 (13.90, 14.00)	13.95 (13.72, 14.09)	13.88 (13.84, 13.98)	13.85 (13.79, 13.95)
Bipolar disorder	7.20 (6.60, 8.60)	8.20 (5.60, 9.40)	7.20 (6.60, 9.40)	6.40 (5.60, 7.00)	13.91 (13.85, 14.10)	13.91 (13.77, 13.99)	13.91 (13.85, 14.06)	13.94 (13.83, 13.97)
ADHD	9.00 (7.80, 9.80)	7.40 (6.20, 9.40)	8.40 (6.80, 9.60)	7.60 (6.40, 8.60)	13.95 (13.85, 14.03)	13.91 (13.76, 14.13)	13.94 (13.83, 14.05)	13.78 (13.73, 13.99)
Conduct disorder	7.80 (5.40, 8.80)	7.00 (6.00, 8.80)	6.60 (5.60, 7.60)	7.20 (4.60, 8.20)	13.92 (13.71, 14.01)	13.95 (13.87, 14.00)	13.78 (13.76, 13.93)	13.91 (13.86, 14.14)
Alcohol or drug abuse	6.80 (5.20, 7.80)	7.40 (4.60, 8.40)	7.80 (7.00, 8.20)	8.00 (5.80, 8.60)	13.91 (13.85, 13.96)	13.89 (13.83, 13.92)	13.90 (13.85, 14.07)	13.87 (13.78, 13.92)

a. Each sensitivity analysis was run 5 times and the medians were reported.

**Table 5.2** Continued

- b. The cut-off score was used to assign increased probability of suicide attempt and completed suicide in the depressed individuals.
- c. 80 is the cut-off point used in the primary analysis model.

**5.4 Discussion**

Utilizing data from different sources, the ABM was able to simulate the course of depression and individuals' care-seeking behaviors while accounting for the complex treatment patterns in the population. The ABM allows one to estimate the potential population-level effects of different suicide prevention interventions without actual implementation data. To the best of our knowledge, this is the first study that evaluates the impact of interventions that reduce undertreatment of depression on preventing suicide in children and adolescents.

The present study only found moderate effect of depression screening on reducing the risk of suicide attempt in the population. So far, studies that evaluate the effectiveness of depression screening in children and adolescents are rare. The United States Preventive Services Taskforce (USPSTF) recommended depression screening among adolescents while acknowledging a moderate certainty for possible net benefit of depression screening due to lack of direct evidence supporting the effect of depression screening in this population.<sup>118</sup> Our study assumed that depression screening achieved the desired implementation goals (i.e., reducing of untreated depression to a certain amount), which indicates that the effect of depression screening on preventing suicide attempt relies on the actual reduction of untreated depression in the population. The model did not account for the implementation process whose success is highly related to factors like healthcare providers' awareness of suicide and communication skills, patients' attitudes

toward depression treatment, family's support and access to health. In addition, it also requires that application of valid depression screening tools with high sensitivity and specificity in the population and carefully designed the strategy of implementing depression screening. The actual impact of depression screening in preventing suicidal behaviors could show more variety in real-world settings with the level of available healthcare resources, education of patients and healthcare providers, and corporation among community, family, and medical care settings.

The CDC identified reducing attrition during treatment as one of the key strategies to prevent suicide.<sup>124</sup> However, reducing attrition during treatment alone did not result in significant decrease in suicide rate or the risk of suicide attempt in the present study. An explanation of lack of population-level effect of reducing attrition during treatment in this study is that only a small group (i.e., those who initiated treatment and would have discontinued the treatment had the intervention were not implemented) was involved. A larger decrease in risk of suicide attempt can be observed when depression screening was implemented together with reducing attrition from treatment for depression or suicide intervention for the depressed individuals, although the magnitude of increase was limited. The increased effect of reducing risk of suicide attempt with combined implementation of depression screening and reducing attrition from treatment for depression suggest that the effect of reducing attrition during treatment on preventing suicidal behaviors may be largely dependent on the proportion of individuals who ever initiate the treatment. but evidence for the efficacy of this intervention among children and adolescents is still rare. Therefore, depression screening

might be a more efficient strategy to prevent suicide attempt when implementation resources are limited.

Among all the interventions examined in the study, the universal suicide intervention in medical care settings revealed the largest effects on reducing the risk of suicide attempt among children and adolescents. This was expected since the universal suicide intervention reached a larger group in the population (i.e., those who utilized medical services) compared with interventions that only focused on the depressed individuals. Ensuring access to health care services is currently a main strategy of preventing suicide, and healthcare settings have been identified as the optimal location for suicide prevention.<sup>125</sup> One systematic approach for preventing suicide within healthcare systems is the Zero Suicide model, which proposes that clinicians should maximize the opportunity to identify and treat patients at elevated risk of suicide.<sup>126</sup> The Zero Suicide model aims to achieve the prevention goal with a series of system-wide strategies by fostering a more suicide-aware environment, training staff for better suicide care provision, promoting engagement of patients and improving continuity and quality of suicide care.<sup>127</sup> Therefore, it must be noted that the effect of the universal suicide intervention estimated in this study does not directly suggest the actual impact of the whole systematic approach proposed by the Zero Suicide model. The results of this study were mainly driven by the average effect of treatment for suicidal behaviors and did not account for the influence of professional skills of healthcare providers, patients' engagement in the treatment, and intervention continuity, which are associated with the ultimate effects of suicide screening and suicide care.

The findings of the present study should be interpreted with caution. Some of the model parameters (e.g., probability of developing depression, probability of initiating treatment for depression) were extrapolated from a national survey conducted 15 years ago (i.e., NCSAS), which may not reflect the most up-to-date estimates for these parameters. The sensitivity analysis suggested robustness of model-estimated suicide rate and risk of suicide attempt to these parameters. Social determinants including access to healthcare, medication beliefs, social stigma (e.g., peer pressure), and community support are also considered important factors associated with mental health service utilization and suicidal behaviors,<sup>128,129</sup> but this ABM was not able to account for the influence of these factors due to limited data. The effects of the interventions were estimated assuming ideal implementation of these interventions that can reach the implementation goals (i.e., decreased prevalence of untreated depression, increased proportion of treatment completion). Interventions were assumed effective once implemented and the intervention effect would last until the end of the study. In real world settings, successful implementation of these interventions can involve a series of activities including effective communication with patients, keeping patients engaged in and coming to care, and continuing follow-up care and it may take some time to achieve the best effects of these interventions. Studies are still needed to identify optimal implementation strategies that help achieve the intervention targets in the population. Finally, the ABM assumes constant probability of developing depression, other psychiatric disorders and suicidal behaviors across different times of a year. In real-world settings, onset of mental health issues and suicidal behaviors are usually associated with season, schooling, and holidays.<sup>130</sup>

## **5.5 Conclusion**

Interventions that reduce undertreatment of depression in the population may have moderate effect in preventing suicide attempt in children and adolescents. Universal suicide intervention in medical care settings may be more effective in reducing suicidal behaviors in the population compared with focusing on reducing undertreatment of depression only.

## **6 Study Summary, Implications, and Strength and Limitations**

### **6.1 Study Summary**

Although undertreatment of depression is common among children and adolescents, the impact of undertreatment of depression on suicide and suicide attempt in the population is largely unknown. Methodological challenges, such as a low suicide rate and the lack of a comprehensive data source, impede the scientific advancement to answer this question. This dissertation research sought to overcome these challenges by using system-science methods, including microsimulation and ABM, to simulate synthetic cohorts and to integrate information from multiple data sources to address this issue. The key research questions are: 1) Is undertreatment of depression associated with an increase in the rate of suicide and the risk of suicide attempt in children and adolescents with depression? 2) Do interventions that reduce undertreatment of depression lower the rate of suicide and risk of suicide attempt of children and adolescents?

The microsimulation model suggested that the longer the duration of antidepressant treatment the greater the effect on reducing suicide rate and the risk of suicide attempt. Completion of acute-phase treatment and continuation-phase treatment may significantly reduce both suicide and suicide attempt among children and adolescents with MDD. An ABM was developed to examine the effects of interventions that reduce undertreatment of depression on preventing suicide and suicide attempt in a synthetic population of children and adolescents aged 10-18. The interventions evaluated in the ABM included depression screening (i.e., to reduce untreated depression in the population), reducing attrition from treatment of depression (i.e., to increase the

proportion of individuals that completed acute-phase treatment of depression), suicide intervention (i.e., suicide screening and treating those at increased risk of suicide) for the depressed individuals and universal suicide intervention in medical care settings. Our results suggest a moderate decrease in suicide attempt using depression screening to reduce untreated depression. Reducing attrition from treatment for depression or suicide intervention for the depressed individuals only did not show a significant effect in reducing suicide rate or the risk of suicide attempt in the population. Compared with interventions that reduce undertreatment of depression in the population, universal suicide intervention, which targets all individuals in seen in medical settings, had larger effects on reducing suicide attempt in children and adolescents.

## **6.2 Implications for Pharmacoepidemiologic Research**

Our study proposed an approach that integrated data and evidence from multiple sources in ABM and microsimulation models to study health outcomes in a population. As Marshall notes, ABM is “*a method to synthesize prior knowledge of a population*” and “*a platform for the integration of diverse evidence sources, including inconsistent or inconclusive scientific information, to support decision making for complex public health problems.*”<sup>131</sup> A strength of these simulation methods is that researchers are able to model possible mechanisms and explore how changes to the systems impact the population.<sup>132</sup> This advances pharmacoepidemiologic research to have a better understanding of the mechanisms that contribute to the best possible treatment effect in the population.<sup>132</sup>

In the era of “big data,” ABM (and other simulation methods) can overcome challenges with data linkages across different data sources, which has limited

advancement of pharmacoepidemiologic research.<sup>76</sup> This dissertation research is a pragmatic example of combining what is known about the efficacy of antidepressant treatment (i.e., trajectories of symptom change over time) and the utilization of antidepressant treatment in the population (e.g., the prevalence of depressed individuals who initiated treatment; the proportion of individuals who completed acute-phase treatment) to estimate completed suicide and suicide attempt in the population. The development of the ABM and microsimulation model uses existing empirical data and published evidence, such as sociodemographic factors, depression severity, and psychiatric comorbidities, to form a reasonable picture of the occurrence of suicide and suicide attempt in children and adolescents. Finally, microsimulation and ABM provide a platform to integrate advanced data science techniques like machine learning and artificial intelligence to help inform decision making for public health policies.

ABM allows one to conduct experiments on synthetic populations when empirical data on actual implementation of the interventions or policies to be evaluated is not available or ethically feasible to collect. For example, evaluation of the impact of depression screening in the population is difficult because data on implementation of depression screening in the population is lacking. In our study, we can estimate the hypothetical effect of depression screening in preventing suicide and suicide attempt children and adolescents by assuming that untreated depression can be reduced with depression screening.

### 6.3 Clinical and Public Health Implications

The significant reduction in suicide rate and risk of suicide attempt with completion of acute-phase (i.e., 12-weeks) of antidepressant treatment suggests that preventing attrition early in the course of treatment can reduce suicide attempts. However, in real world settings, more than 60% of individuals diagnosed with depression are never treated, and, of those who are treated, over 50% discontinue the treatment within the first 12 weeks of initiating an antidepressant.<sup>2,100,101</sup> Lack of regular care providers, patients' negative attitude towards medications, side effects, lack of symptom improvement, severity of depressive symptoms and drug abuse history may affect treatment seeking and dropout.<sup>133–135</sup> Evidence from previous studies supports interventions involving both healthcare providers and patients, e.g., collaborative care, to improve medication adherence and prevent treatment dropout.<sup>3,136,137</sup> Thus, supportive services in addition to suicide prevention intervention may be critical to reduce treatment attrition as a strategy to reduce suicide and suicide attempt among children and adolescents.

Our findings suggest promising results of universal suicide intervention, including suicide screening and treatment for those at elevated risk of suicide, in medical settings. The US Surgeon General and NAASP have set the goal of identifying and treating all persons who need suicide care in both general and mental health care settings.<sup>46</sup> Medical institutions are central locations for suicide prevention. An implication of our study is that promoting access to healthcare is critical because individuals in need of suicide care are more likely to receive treatment for suicide if they are engaged in medical care. Suicidal behaviors are more common among children and adolescents living in areas with

higher poverty and where healthcare facilities and mental health services are limited.<sup>138-</sup>  
<sup>140</sup> The CDC identified lack of access to healthcare services as a key area for intervention  
in reducing suicide in the population.<sup>124</sup> Consequently, the CDC proposes to increase  
mental health service use and reduce treatment attrition by increasing insurance coverage  
for mental health services, reducing provider shortages, and promoting system  
transformation.<sup>124</sup>

Although limited population-level impact was observed for depression screening  
and reducing attrition of depression treatment in this dissertation research, it only  
indicates a marginal effect of treatment extrapolated from efficacy of antidepressants and  
should not be interpreted as limited benefits of these interventions for children and  
adolescents with depression. Given the shortage of mental health specialty providers and  
barriers of access to specialty professionals, there is increasing need for universal  
depression screening and treatment for depression at primary care settings. The American  
Academy of Pediatrics (AAP) published the updated guidelines for depression screening  
for primary care providers in 2018 to help promote depression identification and  
treatment among children and adolescents.<sup>82</sup> In addition to evidence-based treatment for  
depression, depression-related training for primary care providers and established referral  
and collaboration network among healthcare providers and community are considered  
important to improve quality and continuity of depression treatment for children and  
adolescents.<sup>141,142</sup> These factors could potentially affect the results of this dissertation  
research,

The intervention effect estimated with ABM assumed that the interventions  
achieved their goal of implementation. For example, the effect of depression screening

was based on the reduction of untreated depression in the population. Suicide interventions (i.e., suicide screening and treatment) assumed all individuals at elevated risk of suicide (i.e., those with suicidal ideation or prior suicide attempt) can be identified and treated. In real practice, it is important to apply the optimal strategy for implementing interventions (e.g., screening and treatment if necessary) and use validated evidence-based tools for the target population to identify as many individuals as possible who need care. The actual effect of interventions may reveal more heterogeneity in subgroups with different levels of available healthcare resources, beliefs and attitudes towards treatment, and support from family, schools and community. In addition, a core element of the Zero Suicide model is training staff in medical care settings.<sup>127</sup> It comes from the belief that good interactions with healthcare providers may help reduce possible stigma or trauma patients may experience and thus promote trust in healthcare providers.<sup>143</sup> Ensuring privacy during screening can be important for adolescents to discuss their concerns and more actively seek help.<sup>144</sup>

To achieve the goal of screening, it is also important to apply valid and reliable screening scales in real practice. For depression screening, several evidence-based tools such as the PHQ-9,<sup>145</sup> and the modified PHQ-Adolescents,<sup>146</sup> have been available to identify depression symptoms and can be used to identify those in need of care. An example of evidence-based suicide screening tool is the Ask Suicide-Screening Questions (ASQ), which is a 4-question screening with high sensitivity and specificity of detecting suicidal behaviors in pediatric population.<sup>35</sup> The ASQ can be used to determine if additional safety assessment is needed. In 2019, American Academy of Pediatrics sponsored the youth suicide risk screening pathways, which is a strategy to implement

universal suicide intervention among youth in medical settings to achieve optimal screening results.<sup>147</sup> The pathways propose to start initial suicide screening with administration of the ASQ, and conduct a brief suicide safety assessment (BSSA) using the Columbia-Suicide Severity Rating Scale<sup>148</sup> for individuals who screen positive. A full mental health evaluation should be conducted if necessary.

#### **6.4 Strength and Limitations**

Using ABM and microsimulation models to study the impact of undertreatment of depression on suicidal behaviors among children and adolescents has several strengths. First, ABM and microsimulation account for multiple factors influencing suicidal behaviors that cannot be obtained in a single data source. This expands the range of research questions that can be addressed beyond the restriction of a single data source. Although synthesizing evidence from multiple data sources may introduce bias from unmeasured confounders,<sup>87</sup> results of the sensitivity analyses suggest that the model estimates were robust to the influence of unbalanced distributions of unmeasured factors. In addition, we were able to evaluate population outcomes that are rare and challenging to collect in empirical data sources. Second, with the “bottom-up” nature of ABM and microsimulation, we can rely on prior knowledge to model the hypothetical dynamics of care seeking behaviors on individual level while accounting for time-varying characteristics. Compared with other methods that primary focus on macro-level information, ABM and microsimulation lay out the possible mechanism which gives rise to problems and suggest directions for future research. Third, the ABM allows us to estimate the potential population-level impact of different interventions which have not

been examined in real populations. ABM provides a fruitful way to assess various interventions and generate hypothesis for future population-based study.

Notwithstanding the advantages, this dissertation study has several limitations. First, estimates of ABM and microsimulation are only as good as the data used to parameterize the models. Parameters that could not be directly estimated from national surveys had to be extrapolated from the published literature. Much of the evidence was not necessarily generated from a nationally representative population or only based on small samples. The results of the ABM and microsimulation assumed that evidence from different sources are derived from the same representative sample, which might not always be true. This may introduce bias in parameterizing individual dynamics. Second, although the effects estimated from ABM and microsimulation models can be considered a comparison between counterfactual states, causal inference can only be made when all potential determinations are considered.<sup>19</sup> The models developed in this dissertation research did not exhaust all factors related to suicide, including influence of social media, social isolation, environmental stress,<sup>13,106</sup> access to healthcare, medication beliefs, social stigma (e.g., peer pressure), and community support.<sup>128,129</sup> In addition, as discussed in the previous sections, the models estimates were mainly based on average effect of treatment and interventions, omitting the potential influence of behaviors of healthcare providers and individual response to the interventions. Third, we parameterized individual-level behaviors using evidence from clinical trials and population-based studies, which relied on the assumption that the synthetic population behaved in the same way as that in the real population. This may not exhaust all possible behavior patterns in the real population, and the effect in the real-world settings might be different from what is

estimated in the simulation models. Finally, the model estimates are subject to the simulation models and only provide insights of the potential association between undertreatment of depression and suicidal behaviors under the defined settings in the models. The models are a simplification and abstraction of the real world, so the results do not necessarily reflect actual real-world scenarios.

## 7 Future Research

This dissertation research developed a fundamental framework of depression care seeking behaviors in children and adolescents, and it can be expanded to include other components like schools, distribution of healthcare resources and healthcare providers behaviors to have a better understanding of the whole system and work out for best strategies for corporation among these different components. Since COVID-19 pandemic, telehealth has been increasingly widely used for mental health services in children and adolescents. With more data available to describe the characteristics of subgroups with different preference for telehealth, ABM and microsimulation models can be used to investigate how to best deliver mental services to subgroups with different characteristics to improve treatment outcomes in children and adolescents.

The current suicide prevention campaign encourages multi-level prevention that intervene factors from individual, medical institution and community level. For example, in Zero Suicide model, evidence-based therapy for individuals in need of suicide care is just one element in the framework. There are many other elements like fostering system-wide culture and awareness for suicide prevention, staff training, promoting quality and continuity of care, and promoting patients' engagement in suicide care management plan that would be co-implemented with suicide care treatment. ABM can be a useful tool to evaluate the impact of the systematic suicide prevention strategy as a whole on the population.

For pharmacoepidemiologic studies, ABM and microsimulations can be utilized to conduct bias analysis when bias is difficult to control with the available data. The advantage of ABM to develop a system in a bottom-up manner makes it intuitive to

simulate different bias scenarios according to the mechanism of how the bias arises from the study process. The ABM can thus be used to explain how bias changes with other factors that can be accounted for in the study. This can also inform future studies to collect data, whenever possible, to control for certain types of bias.

## **8 Appendices**

### **8.1 Technical Supplement to the Microsimulation for Aim 1**

The microsimulation model was built to simulate the progress of depressive symptoms under different treatment strategies among children and adolescents aged from 10 – 18 diagnosed MDD. The time-horizon of the model is 1 year (52 weeks). A complete simulation run consisted of 52 time-steps (i.e., ticks), and each time-step represented a week.

#### **8.1.1 Model Structure**

##### ***8.1.1.1 Agents and Attributes***

The model only had one type of agents: children and adolescents with MDD. The agents were characterized by baseline sociodemographic and clinical characteristics including age, sex, race/ethnicity, family income, single or no-parent household, parental suicide/suicide attempt, and psychiatric comorbidities (i.e., ADHD, bipolar disorder, conduct disorder/oppositional defiant disorder, alcohol/drug abuse), and previous history of suicidal ideation. Distributions of sociodemographic and clinical characteristics in the simulated agents were assigned according to MEPS and NCSAS to ensure that the simulated agents were representative of the national population. The data sources for determining the distributions of agents' characteristics are listed in Section 7.2.

##### ***8.1.1.2 Treatment Process Overview***

Within 52 weeks, agents could receive depression treatment with various duration from 0 week to 52 weeks. Each time step in the mode represents one week. Suicidal ideation, suicide attempt and completed suicide could occur at any time.

## **8.1.2 Model Parameterization**

### ***8.1.2.1 Baseline Characteristics of Agents***

Age, sex, race/ethnicity were determined first. Age was assigned to each agent to make sure that proportions of children (10-12) and adolescents (13-18) in the simulated agents matched those in national child and adolescent population with MDD. Sex was determined for children and adolescents separately according to sex distributions in each age group. Race/ethnicity was assigned for each age/sex group (i.e., female children, male children, female adolescents, male adolescents) based on race/ethnicity distributions by age and sex. Family income, single or no parent household were assigned based on the distributions of these characteristics by race/ethnicity. Psychiatric comorbidities were assigned based on the distributions of each of the conditions by age and sex.

### ***8.1.2.2 Depressive Symptoms***

#### ***8.1.2.2.1 Baseline Depressive Symptoms***

Because no direct estimates were available for distribution of CDRS-R scores in children and adolescents with MDD on national level, we determined the mean and standard deviation (SD) of CDRS-R scores in the simulated agents in the following way: 1) we identified the proportion of children and adolescents with MDD at general (i.e., non-specialty) and specialty care settings according to published literature. It was estimated that 80% of children and adolescents with MDD were found in special care settings, while 20% only visited general care settings;<sup>149</sup> 2) we assigned CDRS-R scores for agents at specialty care and general care settings separately. The mean and SD of CDRS-R scores in each of the two medical settings were extracted from TADS<sup>69</sup> (for

CDRS-R scores in specialty care settings) and a published study based on a community care sample (for CDRS-R scores in general care settings),<sup>3</sup> respectively (Section 7.2).

#### **8.1.2.2 Depressive Symptoms Change**

##### *Depressive Symptom Change in Treatment Weeks*

CDRS-R scores of agents were programmed to change as a linear function of time. The following function was developed when agents started treatment:

$$\mathbf{[e.q. 1]} \text{ Update Score}_{ij} = \text{Baseline CDRSR score}_i + \beta_{i1} * \ln(\text{tick} * 7) + \varepsilon_{ij}$$

Where  $\text{Update Score}_{ij}$  was the CDRS-R score of the agent  $i$  at week  $j$ . Weeks were represented by ticks (i.e., time-steps).  $\text{Baseline CDRSR score}_i$  was the assigned baseline CDRSR score for agent  $i$ .  $\beta_{i1}$  was the slope of CDRS-R change of agent  $i$ .

To parameterize  $\mathbf{[e.q.1]}$ , we estimated intercepts and slopes separately because of lack of information on covariance between intercepts and slopes. For slopes, we used a two-stage approach to simulate the mixed effects in simulated agents and assigned respective  $\mathbf{[e.q.1]}$  for each agent. The general idea of this approach has two steps: 1) simulate  $\beta_{i1}$  assuming that  $\beta_{i1} = \beta_1 + b_{i1}$ , where  $b_{i1} \sim N(0, \sigma_{b1}^2)$ ; 2) simulate  $\text{Update Score}_{ij}$  using  $\mathbf{[e.q.1]}$  assuming  $\varepsilon_{ij} \sim N(0, 1)$ .

To determine  $\beta_{i1}$  and  $\sigma_{b1}^2$ , we referred to a published study that examined depressive symptom change trajectories using data from TADS.<sup>95</sup> Based on the study, there were three latent groups in CDRS-R trajectories, where the average slope of trajectories (which can be considers as  $\beta_1$  in my study) followed different distributions: 1) high response (i.e., HE) group, where  $\beta_1$  (i.e., fixed effect) was -9.46 and  $\sigma_{b1}^2$  (i.e., variance of random effect) was 3.06 ( $\sigma_{b1}$  was thus 1.75); 2) limited response (i.e. LIM)

group, where  $\beta_1$  was -3.53 and  $\sigma_{b_1}^2$  was 3.06; 3) late response (i.e. LATE) group, where  $\beta_1$  (i.e., fixed effect) was -4.76 and  $\sigma_{b_1}^2$  was 3.06. In the subsequent steps of model building, we will have the agents assigning to each of the three groups.

Intercepts in **[e.q.1]** were baseline CDRS-R scores and are considered strongly associated with the latent groups a patient was most likely to belong to.<sup>95</sup> To determine the appropriate group an agent should be in, the following rules were applied according to published literature:<sup>95</sup> 1) agents with baseline scores larger than 75.51 were assigned to “HE” group; 2) agents with baseline scores between 67.23 and 75.51 were assigned to “LIM” group; 3) agents with baseline scores less than 67.23 were assigned to “LATE” group. The cut-off points to determine score change group were determined based on the proportions of patients and distributions of the CDRS-R scores in each latent group reported in the literature.<sup>95</sup> The following approach was applied to obtain the cut-off points: 1) a sample (n = 10000) was simulated to have 9% of HE, 13% of LIM, and 78% of LATE; 2) for each latent group, CDRS-R scores were simulated based on different distributions (HE: 79.6(7.39); LIM: 70.98(5.67); LATE: 56.01(6.77)); 3) the simulated CDRS-R scores were sorted from highest to lowest, and the cut-off points were the scores at 9%, and 22% rank.

CDRS-R scores of agents that responded to the treatment at Week 12(response was defined as 33% or more decrease in CDRS-R score from baseline.

A new function was developed for agents who did not respond to the treatment (i.e., treatment resistant agents) after week 12:

$$[\mathbf{e.q. 2}] \text{ Update Score}_{ij} = \text{CDRSR score at Week } 12_i + \beta_{i2} * \ln[(\text{tick} - 12) * 7] + \varepsilon_{ij}$$

Where  $\text{Update Score}_{ij}$  was the CDRS-R score of the agent  $i$  at week  $j$  ( $12 < j \leq 52$ ).  $\text{CDRSR score at Week } 12_i$  was the CDRSR score at Week 12 for agent  $i$ .  $\beta_{i2}$  was the re-assigned slope of CDRS-R change of agent  $i$  for time after Week 12.

For treatment resistant agents, Week 12 was considered the new “baseline” from which agents were switched to an increased dose of the current antidepressant, to another antidepressant, augment, and/or add CBT or other psychotherapy. CDRS-R score of treatment resistant agents would change following  $[\mathbf{e.q.2}]$  since Week 13.

Similar with  $[\mathbf{e.q.1}]$ , slopes for  $[\mathbf{e.q.2}]$  were estimated with the two-stage approach with two steps to simulate 1)  $\beta_{i2}$  assuming that  $\beta_{i2} = \beta_2 + b_{i2}$ , where  $b_{i2} \sim N(0, \sigma_{b2}^2)$ , and 2)  $\text{Update Score}_{ij}$  using  $[\mathbf{e.q.2}]$  assuming  $\varepsilon_{ij} \sim N(0, 1)$ .

To determine  $\beta_{i2}$  and  $\sigma_{b2}^2$ , we referred to a published study using data from TORDIA study<sup>91</sup> to examine depressive symptom change trajectories among treatment resistant adolescents with MDD. Consistent with TADS, three latent trajectory groups were observed in TORDIA study. Therefore, the approach of determining  $\beta_{i2}$  was similar with that used for  $\beta_{i1}$ . Treatment resistant agents were assigned to one of the following groups at the end of week 12: 1) agents with week 12 CDRS-R scores larger than 65.34 were assigned to the no response (i.e., “NO”) group where  $\beta_2$  (i.e., fixed effect) was -3.37 and  $\sigma_{b2}^2$  (i.e., variance of random effect) was 3.06; 2) agents with week 12 CDRS-R scores between 52.13 and 65.34 were assigned to the steady improvement (i.e., “SLOW”) group where  $\beta_2$  was -5.14 and  $\sigma_{b2}^2$  was 3.06; 3) agents with week 12

CDRS-R scores less than 52.13 were assigned to rapid remission (i.e., “GO”) group where  $\beta_2$  was -4.98 and  $\sigma_{b_2}^2$  was 3.06. Because TORDIA trajectory study did not report fixed and random effects of slopes directly, the fixed effects of slopes for each latent group were thus solved based on mean CDRS-R scores at baseline and week 72 reported in the study, with the following equation:

$$[\mathbf{e.q.3}] \text{ Mean CDRSR Score at week 72} = \text{Mean CDRSR Score at baseline} + \beta_2 * \ln(72 * 7)$$

$\sigma_{b_2}^2$  for treatment resistant agents was assumed to be the same with non-resistant agents (i.e.,  $\sigma_{b_1}^2$ ).

The cut-off points for group assignment among treatment resistant agents were determined in a similar way used in baseline group assignment. Based on the proportions of patients in each latent group and CDRS-R score distributions in each latent group reported in TORDIA trajectory study<sup>91</sup>, the following approach was applied to obtain cut-off points for group assignment: 1) a sample (n = 10000) was simulated to have 27% of “GO”, 48% of “SLOW”, and 25% of “NO”; 2) for each group, CDRS-R scores are simulated based on the distributions observed in respective groups (GO: 52.2(8.03); SLOW: 58.3(8.8); NO: 67.1(10.1)); 3) the simulated CDRS-R scores were sorted from highest to lowest, and the cut-off points were the scores at 25%, and 73% rank.

Because the literature for determining treatment effect on treatment-resistant agents only reported results on pooled patients across different treatment arms, an average effect of various treatment options for switching was used when determining the parameters for [e.q.2].

### *Depressive Symptom Change in Non-treatment Weeks*

The following two functions were developed for CDRS-R score change when agents were off the treatment since Week  $n_k$  ([e.q.4]) and for CDRS-R score change from week 1 under no treatment strategy ([e.q.5]):

$$[\mathbf{e.q.4}] \text{ Update Score}_{ij} = \text{CDRSR Score}_{i,j-1} + \beta_{i3} * \ln \left[ \frac{\text{tick}}{\text{tick}-1} \right] + \varepsilon_{ij}$$

Where  $n_k < j \leq 52$ .

$$[\mathbf{e.q.5}] \text{ Update Score}_{ij} = \text{baseline CDRSR score}_i + \beta_{i3} * \ln(\text{tick} * 7) + \varepsilon_{ij}$$

Where  $1 \leq j \leq 52$ .

We determined  $\beta_{i3}$  using the same two-stage approach as we used for [e.q.2]. We referred to a published study that enrolled untreated controls of adolescents diagnosed with depression.<sup>96</sup> The fixed effect of slopes of depressive symptom change under no treatment was solved using the mean CDRS-R scores at baseline and week 36 (9 months) using the following equation:

$$[\mathbf{e.q.6}] \text{ Mean CDRSR Score at week 36} = \text{Mean CDRSR Score at baseline} + \beta_3 * \ln(36 * 7)$$

The solved  $\beta_3$  was -1.84. We still assumed the variance of slope random effects to be 3.06.

### **8.1.2.3 Suicidality**

#### *Suicidal Ideation*

The probability of having suicidal ideation during model course was estimated using the following equation:

$$\begin{aligned}
[\mathbf{e.q.7}] \text{logit}(P_{\text{suicidal ideation } i}) = & -4.766 + 0.1314 * \text{age}_i - 0.4197 * \\
& \text{female}_i + 0.1491 * \text{hisp}_i - 0.225 * \text{nhb}_i + 0.4995 * \text{nhw}_i - 0.2456 * \\
& \text{lowIncome}_i + 0.1215 * \text{midIncome}_i + 0.9598 * \text{adAbuse}_i + 0.41 * \\
& \text{moderateDepress}_i + 2.04 * \text{severeDepress}_i + 0.4413 * \text{bipolar}_i + 0.3592 * \\
& \text{adhd}_i + 0.6042 * \text{cdodd}_i + 0.1839 * \text{singleParent}_i + 0.4994 * \text{parentSuicide}_i
\end{aligned}$$

Where “age” is a continuous variable representing agents’ age at the current time-step, “male” is the sex (1 = female, 0 = male), “hisp”/”nhb”/”nhw” are dummy variables for race/ethnicity (Hispanic (hisp = 1, nhb = 0, nhw = 0), non-Hispanic Black (hisp = 0, nhb = 1, nhw = 0), non-Hispanic White (hisp = 0, nhb = 0, nhw = 1) and other (hisp = 0, nhb = 0, nhw = 0)), “lowIncome”/”midIncome” are dummy variables for household income (low income (lowIncome = 1, midIncome = 0), middle income (lowIncome = 0, midIncome = 1), high income (lowIncome = 0, midIncome = 0)), “adAbuse” is past year alcohol or drug abuse, “moderateDepress” is mild to moderate depression (35 <= CDRS-R Score < 60), “severeDepress” is severe depression (CDRS-R score >= 60), bipolar was diagnosis of bipolar disorder at baseline, “adhd” is diagnosis of ADHD at baseline, “cdodd” is diagnosis of conduct disorder or oppositional defiant disorder at baseline, “singleParent” is whether the agent was from a household with single or no parent, and “preantSuicide” is whether any of the parents had suicide attempt or completed suicide before.

The coefficients of the characteristics, except for those for moderate and severe depression, were estimated from a logistic regression model fitted with information from NCSAS. Since the survey does not provide information on the association between suicidal ideation and severity of depression, coefficients for moderate and severe

depression were estimated from published literature. We referred to the study <sup>115</sup> that reported odds ratios (OR) of suicidal behaviors comparing patients with different depression severity levels, and extracted coefficients based on reported ORs.

The probability of suicidal ideation of each agent was calculated as

$$P_{suicidal\ ideation\ i} = \frac{\exp^{logit(P_{suicidal\ ideation\ i})}}{1 + \exp^{logit(P_{suicidal\ ideation\ i})}}$$

The intercept of [e.q.7] was calibrated to produce a 60% of decrease of suicidal ideation after 12 weeks when SSRI treatment in the model.<sup>69</sup>

#### Suicide attempt and completed suicide

The probability of completed suicide for agents without suicidal ideation and suicide attempt when MDD had not recovered was estimated using Bayesian formular below:

$$[e.q.8] P(\text{Suicide} = 1 \mid \text{Depression} = 1, \text{Suicidal Ideation} = 0, \text{Suicide Attempt} = 0, \text{Age, Sex}) = \frac{P(\text{Depression} = 1 \mid \text{Suicide} = 1) * P(\text{Suicide} = 1 \mid \text{Age, Sex})}{P(\text{Depression} = 1 \mid \text{Age, Sex})}$$

Where  $P(\text{Depression} = 1 \mid \text{Suicide} = 1)$  represents the probability of having depression among children and adolescents who completed suicide.<sup>30,98</sup> We assumed  $P(\text{Depression} = 1 \mid \text{Suicide} = 1) = 0.6$ .  $P(\text{Suicide} = 1 \mid \text{Age, Sex})$  represents the overall suicide rates among children and adolescents by age and sex,<sup>150</sup> and  $P(\text{Depression} = 1 \mid \text{Age, Sex})$  represents prevalence of MDD among children and adolescents by age and sex (estimated from MEPS data 2016-2018).

Similarly, if MDD recovered, the probability of completed suicide without previous suicidal ideation or suicide attempt was estimated as below:

$$[\mathbf{e.q.9}] P(\text{Suicide} = 1 \mid \text{Depression} = 0, \text{Suicidal Ideation} = 0, \text{Suicide Attempt} = 0, \text{Age}, \text{Sex}) = (P(\text{Depression} = 0 \mid \text{Suicide} = 1) * P(\text{Suicide} = 1 \mid \text{Age}, \text{Sex})) / P(\text{Depression} = 0 \mid \text{Age}, \text{Sex})$$

Where  $P(\text{Depression} = 0 \mid \text{Suicide} = 1)$  represents the probability of not having depression among children and adolescents who conducted suicide (calculated as  $1 - P(\text{Depression} = 1 \mid \text{Suicide} = 1)$ ),  $P(\text{Suicide} = 1 \mid \text{Depression} = 0, \text{Age}, \text{Sex})$  represents the overall suicide rates among children and adolescents without MDD by age and sex,<sup>150</sup> and  $P(\text{Depression} = 0 \mid \text{Age}, \text{Sex})$  represents non-depressed children and adolescents by age and sex (estimated from MEPS data 2016-2018).

In this microsimulation model, we assumed that having suicidal ideation or suicide attempt would increase the probability of completed suicide. We referred to a published literature that examined suicide rate after previous suicide attempt and suicidal ideation,<sup>99</sup> and the probability of suicide following suicidal ideation or suicide attempt was calculated as below:

$$[\mathbf{e.q.10}] P(\text{Suicide} = 1 \mid \text{Age}, \text{Sex}, \text{Suicidal ideation}=1, \text{Suicide Attempt} = 0) = P(\text{Suicide} = 1 \mid \text{Depression} = 1, \text{Age}, \text{Sex}) * 3$$

$$[\mathbf{e.q.11}] P(\text{Suicide} = 1 \mid \text{Age}, \text{Sex}, \text{Suicide Attempt}=1) = P(\text{Suicide} = 1 \mid \text{Depression} = 1, \text{Age}, \text{Sex}) * 4$$

Where 3 was extracted from the OR that compared the suicide rate among those who expressed suicidal ideation with that among those who did not, and 4 was extracted

from the OR that compared the suicide rate among those who had previous suicide attempt with that among those who did not.

### **8.1.3 Model Calibration**

Although there is no longitudinal data to calibrate the model based on national child and adolescent population with MDD in one-year follow up, we calibrated some critical model-reproduced outcomes against empirically observed values, which include:

- (1) Decrease of suicidal ideation from baseline to Week 12.
- (2) Response rate at Week 12.
- (3) Remission rate at Week 12.
- (4) Remission rate at Week 36.

TADS reported that patients (including those on fluoxetine, CBT, combined fluoxetine and CBT, and placebo) with at least some suicidal ideation decreased 60% from baseline to Week 12 after treatment.<sup>69</sup> Therefore, we calibrated the model by tuning the intercept of [e.q.7] to have 60% decrease in the proportion of agents who have suicidal ideation from baseline to Week 12.

The response rate for antidepressant treatment at Week 12 reported in TADS trial is 60%.<sup>69</sup> Usually, week-12 response to treatment was defined by a certain amount of decrease in the CDRS-R scores from baseline to Week 12. We calibrated the model by testing different definitions of response treatment until the Week 12 response rate was 60%, which was 33% decrease in CDRS-R score from baseline score to Week 12.

To calibrate remission rate at Week 12, we tested a series of values of probability of relapse during Week 1-12 with  $\pm 0.0001$  intervals around the literature-extracted value

and selected the one (0.0061) that produced a Week-12 remission rate that was closest to the empirically observed value. After Week 12, we calibrated the probability of relapse during Week 13-36 of responders and treatment-resistant agents separately until remission rate at Week 36 was closed to empirically observed value.

## 8.2 Aim 1: Data Source and Input Parameters of Microsimulation Model

**Table 8.1** Data Sources for the Microsimulation Model

Parameter	Definition	Data Source
Age (baseline)	Range: 10 – 17 (continuous)	MEPS 2016-2018
Sex	Female/Male	MEPS 2016-2018
Race/ethnicity	Non-Hispanic White/Non-Hispanic Black/Hispanic/Other	MEPS 2016-2018
Family Income	High Income (> 400% poverty line) Middle Income (200% - 400% poverty line) Low Income (< 200% poverty line)	MEPS 2016-2018
Single or No Parent Household	Yes/No	MEPS 2016-2018
Parental suicide/suicide attempt	Yes/No	NCSAS
ADHD	Yes/No	MEPS (2016-2018)
Anxiety Disorder	Yes/No	MEPS (2016-2018)
Bipolar Disorder	Yes/No	MEPS (2016-2018)
CD/ODD	Yes/No	MEPS (2016-2018)
Alcohol/Drug Abuse	Yes/No	NCSAS
Medical Care Settings	Primary Care/Specialty Care	Lu W. et al 2020
CDRS-R Score		
Primary Care Setting	Mean: 47.1 Standard Deviation: 10.25	Richardson LP et al. <sup>3</sup>
Specialty Care Setting	Mean: 60.1 Standard Deviation: 10.39	TADS trial
Probability of Relapse		
Weeks prior to Week 12 (Acute phase treatment)	0.0061 (weekly)	Kennard BD et al.2009 <sup>88</sup>
Weeks from Week 13 to Week 36 (Continuation phase treatment)	Non-treatment-resistant agents: 0.001 (weekly) Treatment-resistant agents: 0.005 (Weekly)	Calibrated.
Maintenance phase (antidepressant treatment)	Non-treatment-resistant agents: 0.0058 (weekly) (calibrated) Treatment resistant agents: 0.02 (weekly) (calibrated)	Chueng A et al. 2008 <sup>151</sup> and calibrated

**Table 8.1** continued

No treatment administered	0.0133 (weekly in first 36 weeks), 0.0192 (weekly after 36 weeks)	Kennard BD et al.2009 <sup>88</sup> , Chueng A et al. 2008 <sup>151</sup>
Probability of Suicide Attempt (MDD not recovered)		
With suicidal ideation	0.0216	Simon GE et al. 2019 <sup>152</sup>
Without suicidal ideation	0.0007	Simon GE et al. 2019 <sup>152</sup>
Probability of Suicide Attempt (MDD recovered)		
With suicidal ideation	0.0056	NCSAS
Without suicidal ideation	0	Assumed
Probability of Completed Suicide (MDD not recovered)		
Female, without suicidal ideation or suicide attempt	Age < 13: 0.26/100000 Age >=13: 0.90/100000	Calculated [e.q.8]
Female, with suicidal ideation but no suicide attempt	Age < 13: 0.60/100000 Age >=13: 2.71/100000	Calculated [e.q.10]
Female, with suicide attempt	Age < 13: 1.02/100000 Age >=13: 3.61/100000	Calculated [e.q.11]
Male, without suicidal ideation or suicide attempt	Age < 13: 0.82/100000 Age >=13: 3.01/100000	Calculated [e.q.8]
Male, with suicidal ideation but no suicide attempt	Age < 13: 1.92/100000 Age >=13: 9.03/100000	Calculated [e.q.10]
Male, with suicide attempt	Age < 13: 3.27/100000 Age >=13: 12.03/100000	Calculated [e.q.11]
Probability of Completed Suicide (MDD recovered)		
Female, without suicidal ideation or suicide attempt	Age < 13: 0.01/100000 Age >= 13: 0.04/100000	Calculated [e.q.9]
Female, with suicidal ideation but no suicide attempt	Age < 13: 0.02/100000 Age >= 13: 0.11/100000	Calculated [e.q.10]
Female, with suicide attempt	Age < 13: 0.02/100000 Age >= 13: 0.15/100000	Calculated [e.q.11]

**Table 8.1** continued

Male, without suicidal ideation or suicide attempt	Age < 13: 0.01/100000 Age >= 13: 0.07/100000	Calculated [e.q.9]
Male, with suicidal ideation but no suicide attempt	Age < 13: 0.03/100000 Age >= 13: 0.22/100000	Calculated [e.q.10]
Male, with suicide attempt	Age < 13: 0.04/100000 Age >= 13: 0.29/100000	Calculated [e.q.11]

**Table 8.2** Summary of Input Model Parameters for Baseline Sociodemographic and Clinical Characteristics of the Synthetic Population of the Microsimulation Model

Parameter	Attribute Values	Sources
	%	
Age		
10 - 12	25%	MEPS (2016 -2018)
13 - 17	75%	
Sex		
Female	60%	MEPS (2016 – 2018)
Male	40%	
Race Ethnicity		
Non-Hispanic White	63%	MEPS (2016 – 2018)
Non-Hispanic Black	6%	
Hispanic	23%	
Other	8%	
Psychiatric Comorbidity		
Age 10-12, Male		
ADHD	32%	MEPS (2016 – 2018)
Bipolar disorder	2%	
CD/ODD	6%	
Alcohol/drug abuse	25%	NCSAS <sup>a</sup>
Age 10-12, Female		
ADHD	28%	MEPS (2016 – 2018)
Bipolar disorder	5%	
CD/ODD	5%	
Alcohol/drug abuse	20%	NCSAS <sup>a</sup>
Age 13 - 18, Male		
ADHD	41%	MEPS (2016 – 2018)
Bipolar disorder	9%	
CD/ODD	2%	
Alcohol/drug abuse	25%	NCSAS
Age 13 - 18, Female		
ADHD	28%	MEPS (2016 – 2018)
Bipolar disorder	3%	
CD/ODD	8%	
Alcohol/drug abuse	20%	NCSAS

**Table 8.2** continued

Parental suicide attempt/suicide	6%	NCSAS
Single-parent household or not living with parents	51%	MEPS (2016 – 2018)
Household poverty level		
Low income (< 200% poverty line)	40%	MEPS (2016 – 2018)
Middle income (200% - 400% poverty line)	27%	
High income (> 400% poverty line)	34%	
	Mean (Standard Deviation)	
CDRS-R Scores	58 (10)	Section 8.1.2.2

- a. NCSAS only provides information on adolescents aged 13 or older. Therefore, alcohol/drug abuse in children was assumed the same with adolescents in the model.

### 8.3 Aim 2: Data Sources and Input Parameters of the ABM

**Table 8.3** Model Parameters, Value Assignment Rules, Update Rules and Data Sources for Parameterization of the ABM

Parameter	Values	Attribute assignment rules	Update Rules	Data sources
<b>Characteristics of Individuals</b>				
Age	10-18 (in months)	Input at initialization.	Age increased by one month at each time step.	MEPS 2016-2018
Sex	Male; Female	Input at initialization.	Remain unchanged.	MEPS 2016-2018
Race/ethnicity	Non-Hispanic White; Non-Hispanic Black; Hispanic; Other.	Input at initialization.	Remain unchanged.	MEPS 2016-2018
Household income	Low income (< 200% poverty line)	Input at initialization.	Remain unchanged.	MEPS 2016-2018
	Middle income (200% - 400% poverty line)	Input at initialization.	Remain unchanged.	MEPS 2016-2018
	High income (> 400% poverty line)	Input at initialization.	Remain unchanged.	MEPS 2016-2018
Single or no parents household	Yes/No	Input at initialization.	Remain unchanged.	MEPS 2016 - 2018
Parental suicide or suicide attempt	Yes/No	Input at initialization.	Remain unchanged.	NCSAS
Parental mental conditions				
Father mental conditions	Yes/No	Input at initialization.	Remain unchanged.	NCSAS
Mother mental conditions	Yes/No	Input at initialization.	Remain unchanged.	NCSAS

**Table 8.3** continued

Probability of dying	0-1	Assigned based on age (under 15 years old and 15 years or older)	Re-assigned at each time step.	US National Census 2016
Probability of mental illness				
Depression	0-1	Calculate based on age, sex, race/ethnicity, household income, single or no parental household, father's mental conditions, mother's mental conditions, status of bipolar disorder, anxiety, ADHD, conduct disorder, and alcohol or drug abuse.	Re-calculated at each time step.	MEPS 2016-2018
Bipolar disorder	0-1	Calculate based on age, sex, race/ethnicity, household income, single or no parental household, father's mental conditions, and mother's mental conditions, by depression status.	Re-calculated at each time step.	MEPS 2016-2018
Anxiety	0-1		Re-calculated at each time step.	MEPS 2016-2018
ADHD	0-1		Re-calculated at each time step	MEPS 2016-2018
CD/ODD	0-1		Re-calculated at each time step.	MEPS 2016-2018
Alcohol or drug abuse	0-1		Re-calculated at each time step.	MEPS 2016-2018

**Table 8.3** continued

Probability of continuing the depression treatment	0-1	Calculated based on alcohol or drug abuse, ADHD and severity of depression.	Re-calculated at each time step after agents had initiated depression treatment.	Timlin U et al. 2015 <sup>113</sup>
CDRS-R Score (baseline)	35-113	Baseline CDRS-R score for agents that developed depression was assigned based on the estimated distribution of CDRS-R scores in depressed population.	Assigned when agents developed depression.	Appendix Section 8.1.2.2
CDRS-R score monthly change	See Appendix Section 8.1.2.2	CDRS-R score changed as a function of the natural log of days since depression by treatment status: 1) on treatment; 2) off treatment.	Re-assigned at each time step based on agents' treatment status.	Appendix Section 8.1.2.2
Probability of outpatient visits	0-1	Calculated based on age, sex, race/ethnicity, household income by depression status.	Re-calculated at each time step.	
Probability of emergency visits	0-1		Re-calculated at each time step.	
Probability of hospitalization	0-1		Re-calculated at each time step.	

**Table 8.3** continued

Probability of suicidal ideation	0-1	Calculated based on age, sex, race/ethnicity, household income, single or no parents household, parental suicide or suicide attempt, severity of depression, psychiatric comorbidities (ADHD, bipolar disorder, alcohol and drug abuse, CD/ODD).	Re-calculated at each time step.	
Probability of attempting suicide	0-1	Assigned based on depression status and suicidal ideation status.	Re-assigned at each time step.	Appendix Section 8.1.2.3
Probability of completed suicide	0-1	Assigned based on age, sex, depression status, suicidal ideation status and previous suicide attempt.	Re-assigned at each time step.	Appendix Section 8.1.2.3

**Table 8.4** Values of Input Parameters and Parameterized Equations Applied in the Model

<b>Model Parameters</b>	<b>Values</b>
Age	10-12: 42% 13-17: 58%
Sex	Male: 52% Female: 58%
Race/ethnicity	Non-Hispanic White: 49% Non-Hispanic Black: 16% Hispanic: 24% Other: 11%
Household income	
Low income (< 200% poverty line)	38%
Middle income (200% - 400% poverty line)	33%
High income (> 400% poverty line)	25%
Single or no parents household	35%
Parental suicide or suicide attempt	3%
Parental mental conditions	
Father mental conditions	10%
Mother mental conditions	18%
Probability of dying	
<15 years old	1.3/100000 (1 month)
≥15 years old	6.6/100000 (1 month)
Equation (1)	Logit ( $\mu_{(\text{depression}=1, 1 \text{ year})}$ ) = -3.689 + 0.085*age + (-0.104)*male + (-0.334)*nhw + 0.018*nhb + (-0.035)*hisp + (-0.146)*lowIncome + (-0.134)*midIncome + (-0.798)*singleParent + 0.608*fathermental + 1.088*mothermental + 0.852*bipolar + 0.525*ADHD + 1.075*cdodd + 2.017*anxiety + 0.436*adAbuse
Equation (4)	Logit( $\mu_{(\text{treatment} = 1, 1 \text{ year})}$ ) = -2.40 + 0.006*age + male*(0.2562) + hisp*(-1.048) + nhb*(-0.8702) + nhw*(0.3692) + lowIncome*(-0.2275) + midIncome*(0.0752) + singleParent*(0.5599) + fathermental*(-0.0118) + mothermental*0.312 + mental*(-0.0776)
Equation (7)	Logit ( $\mu_{(\text{drop-out}=1, 1 \text{ year})}$ ) = 1.2 + (-0.198)*adAbuse + (-0.4943)*adhd + (-0.4005)*severeDepress
Equation (12)	

**Table 8.4** continued

Among the depressed	$\text{Logit } (\mu_{(\text{bipolar}=1, 1 \text{ year})}) = -4.39 + 0.4325*\text{child} + 0.7671*\text{male} + 1.4777*\text{hisp} + (-14.336)*\text{nhb} + 0.5204*\text{nhw} + (-0.3227)*\text{lowIncome} + (-2.1362)*\text{midIncome} + 0.5206*\text{singleParent} + 0.0709*\text{fathermental} + 0.6065*\text{mothermental}$
	$\text{Logit } (\mu_{(\text{ADHD}=1, 1 \text{ year})}) = -3.11 + 0.1851*\text{child} + 0.5866*\text{male} + 1.1620*\text{hisp} + 0.7555*\text{nhb} + 2.2763*\text{nhw} + 0.6750*\text{lowIncome} + 0.0966*\text{midIncome} + (-0.6773)*\text{singleParent} + (-0.6952)*\text{fathermental} + 0.7656*\text{mothermental}$
	$\text{Logit } (\mu_{(\text{conduct disorder}=1, 1 \text{ year})}) = -5.28 + (-0.0677)*\text{child} + (-1.3373)*\text{male} + (-1.0993)*\text{hisp} + (-0.7986)*\text{nhb} + (0.6521)*\text{nhw} + (-1.2049)*\text{lowIncome} + (-0.8100)*\text{midIncome} + 2.4388*\text{singleParent} + 1.2940*\text{fathermental} + 2.1972*\text{mothermental}$
	$\text{Logit } (\mu_{(\text{anxiety}=1, 1 \text{ year})}) = -0.081 + (-0.0957)*\text{child} + (-0.6614)*\text{male} + (-0.2516)*\text{hisp} + (-1.9338)*\text{nhb} + 0.4441*\text{nhw} + (-0.8071)*\text{lowIncome} + (-0.1133)*\text{midIncome} + 0.7325*\text{singleParent} + 0.2095*\text{fathermental} + (-0.5628)*\text{mothermental}$
	$\text{Logit } (\mu_{(\text{alcohol/drug abuse}=1, 1 \text{ year})}) = -2.079 + (-0.011)*\text{child} + 0.214*\text{male} + (0.869)*\text{nhw} + (-0.293)*\text{nhb} + 1.257*\text{hisp} + (-0.257)*\text{lowIncome} + (-0.053)*\text{midIncome} + (-0.357)*\text{singleParent} + 0.706*\text{fathermental} + 0.056*\text{mothermental}$
Among the nondepressed	$\text{Logit } (\mu_{(\text{bipolar}=1, 1 \text{ year})}) = -4.39 + 0.9834*\text{child} + 0.2828*\text{male} + (-1.5008)*\text{hisp} + (-2.6462)*\text{nhb} + (-0.5630)*\text{nhw} + 1.7849*\text{lowIncome} + 1.9161*\text{midIncome} + 0.7996*\text{singleParent} + (-0.1837)*\text{fathermental} + 1.0058*\text{mothermental}$
	$\text{Logit } (\mu_{(\text{ADHD}=1, 1 \text{ year})}) = -3.105 + (-0.2982)*\text{child} + 0.9418*\text{male} + 0.00789*\text{hisp} + 0.4007*\text{nhb} + 0.8440*\text{nhw} + 0.2130*\text{lowIncome} + (-0.0778)*\text{midIncome} + 0.3539*\text{singleParent} + 0.3941*\text{fathermental} + 0.7795*\text{mothermental}$
	$\text{Logit } (\mu_{(\text{conduct disorder}=1, 1 \text{ year})}) = -5.276 + (-0.3431)*\text{child} + 0.8489*\text{male} + 0.3793*\text{hisp} + 0.1098*\text{nhb} + 0.7448*\text{nhw} + 0.5535*\text{lowIncome} + (-0.3037)*\text{midIncome} + 0.2092*\text{singleParent} + 0.4282*\text{fathermental} + 1.1450*\text{mothermental}$

**Table 8.4** continued

	$\text{Logit } (\mu_{(\text{anxiety}=1, 1 \text{ year})}) = -0.081 + 0.1696*\text{child} + (-0.3188)*\text{male} + 0.0631*\text{hisp} + (-0.4254)*\text{nhb} + 1.4326*\text{nhw} + 0.00042*\text{lowIncome} + (-0.1611)*\text{midIncome} + 0.0498*\text{singleParent} + 0.9132*\text{fathermental} + 1.1522*\text{mothermental}$
	$\text{Logit } (\mu_{(\text{alcohol/drug abuse}=1, 1 \text{ year})}) = -2.079 + 0.5481*\text{child} + 0.4541*\text{male} + 0.5213*\text{hisp} + (-0.6268)*\text{nhb} + 1.0474*\text{nhw} + (-0.3791)*\text{lowIncome} + (-0.2804)*\text{midIncome} + 0.2775*\text{singleParent} + 1.0327*\text{fathermental} + 0.749*\text{mothermental}$
Equation (15)	
Outpatient visits	
Among the depressed	$\text{Log } (\mu_{(\text{outpatient} = 1)/1 \text{ year}}) = 0.339 + (-0.0709)*\text{age} + (0.7209)*\text{male} + (-0.7374)*\text{nhw} + (-0.6024)*\text{nhb} + (-0.1397)*\text{hisp} + (-0.7956)*\text{lowIncome} + (-1.1663)*\text{midIncome}$
Among the nondepressed	$\text{Log } (\mu_{(\text{outpatient} = 1)/1 \text{ year}}) = -3.186 + (0.0353)*\text{age} + (0.0991)*\text{male} + (1.1040)*\text{nhw} + (0.1211)*\text{nhb} + (0.4544)*\text{hisp} + (-0.0019)*\text{lowIncome} + (-0.0862)*\text{midIncome}$
Emergency visits	
Among the depressed	$\text{Log } (\mu_{(\text{emergency} = 1)/1 \text{ year}}) = 0.150 + (-0.1571)*\text{age} + (0.7894)*\text{male} + (-0.3319)*\text{nhw} + (-0.4554)*\text{nhb} + (0.0925)*\text{hisp} + (-0.0828)*\text{lowIncome} + (-0.5221)*\text{midIncome}$
Among the nondepressed	$\text{Log } (\mu_{(\text{emergency} = 1)/1 \text{ year}}) = -2.934 + (0.0513)*\text{age} + (-0.0185)*\text{male} + (-0.1201)*\text{nhw} + (-0.1057)*\text{nhb} + (-0.3181)*\text{hisp} + (0.4870)*\text{lowIncome} + (0.2492)*\text{midIncome}$
Inpatient visits	
Among the depressed	$\text{Log } (\mu_{(\text{inpatient}= 1)/1 \text{ year}}) = -2.277 + (-0.0861)*\text{age} + (1.1673)*\text{male} + (-0.2681)*\text{nhw} + (-0.0835)*\text{nhb} + (-0.3972)*\text{hisp} + (0.0442)*\text{lowIncome} + (-0.6281)*\text{midIncome}$
Among the nondepressed	$\text{Log } (\mu_{(\text{inpatient}= 1)/1 \text{ year}}) = -6.127 + (0.0944)*\text{age} + (0.0790)*\text{male} + (0.3923)*\text{nhw} + (0.0468)*\text{nhb} + (0.3828)*\text{hisp} + (0.4247)*\text{lowIncome} + (0.1272)*\text{midIncome}$
Probability of Suicide Attempt (depressed)	
With suicidal ideation	0.0216
Without suicidal ideation	0.0007

**Table 8.4** continued

Probability of Suicide Attempt (nondepressed)	
With suicidal ideation	0.0056
Without suicidal ideation	0
Probability of Suicide (depressed)	
Female, without suicidal ideation or suicide attempt	Age < 13: 1.11/100000 (1 month) Age ≥ 13: 3.90/100000 (1 month)
Female, with suicidal ideation but no suicide attempt	Age < 13: 2.60/100000 (1 month) Age ≥ 13: 11.66/100000 (1 month)
Female, with suicide attempt	Age < 13: 4.42/100000 (1 month) Age ≥ 13: 15.52/100000 (1 month)
Male, without suicidal ideation or suicide attempt	Age < 13: 3.53/100000 (1 month) Age ≥ 13: 12.95/100000 (1 month)
Male, with suicidal ideation but no suicide attempt	Age < 13: 8.28/100000 (1 month) Age ≥ 13: 38.36/100000 (1 month)
Male, with suicide attempt	Age < 13: 14.05/100000 (1 month) Age ≥ 13: 50.81/100000 (1 month)
Probability of Suicide (nondepressed)	
Female, without suicidal ideation or suicide attempt	Age < 13: 0.02/100000 (1 month) Age ≥ 13: 0.16/100000 (1 month)
Female, with suicidal ideation but no suicide attempt	Age < 13: 0.06/100000 (1 month) Age ≥ 13: 0.47/100000 (1 month)
Female, with suicide attempt	Age < 13: 0.09/100000 (1 month) Age ≥ 13: 0.63/100000 (1 month)
Male, without suicidal ideation or suicide attempt	Age < 13: 0.04/100000 (1 month) Age ≥ 13: 0.31/100000 (1 month)
Male, with suicidal ideation but no suicide attempt	Age < 13: 0.12/100000 (1 month) Age ≥ 13: 0.93/100000 (1 month)
Male, with suicide attempt	Age < 13: 0.16/100000 (1 month) Age ≥ 13: 1.24/100000 (1 month)
CDRS-R score monthly change ( $\beta_{s_{ij}}$ ) Equations (10) and (11)	Mean (variance)
$\beta_{s_{ij}}$ in months with treatment	
Non-treatment resistant	High response: -9.46 (3.06); Late response: -4.76 (3.06); Limited response: -3.53 (3.06)
Treatment resistant	High response: -4.98 (3.06); Late response: -5.14 (3.06); Limited response: -3.37 (3.06)

**Table 8.4** continued

$\beta_{s_{ij}}$ in months without treatment	-1.84 (3.06)
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#### 8.4 Aim 3: Sensitivity Analysis Results and Other Model-Estimated Results

**Table 8.5** Sensitivity Analysis with a Cut-off Point 0 in the CDRS-R Scores<sup>a</sup>

	Change of Suicide Rate (95%CI)	Change of Risk of Suicide Attempt (95% CI)
<b>Depression Screening</b>		
Reduction of untreated depression		
20%	0.40 (-1.20, 3.00)	-0.34 (-0.42, -0.25)
50%	-0.80 (-3.20, 4.80)	-0.47 (-0.69, -0.29)
80%	-1.20 (-3.80, 1.20)	-0.73 (-0.93, -0.64)
Reducing Attrition During Treatment	-1.00 (-5.20, 4.40)	-0.23 (-0.59, -0.18)
Suicide intervention on the depressed	-0.80 (-2.00, 3.20)	-0.31 (-0.40, -0.29)
Universal suicide intervention		
20%	-2.20 (-3.00, 1.00)	-0.71 (-0.98, -0.70)
50%	-1.80 (-2.40, -0.20)	-1.61 (-1.83, -1.57)
80%	-1.80 (-3.60, 3.40)	-2.47 (-2.47, -2.37)

a. The cut-off point was a point above which defined the increased probability of completed suicide and suicide attempt.

**Table 8.6** Other Model Estimates from the ABM<sup>a</sup>

	Model-Estimated Results (95% CI) <sup>a</sup>
Risk of Suicidal Ideation (%)	
Depressed individuals	45.7 (40.2, 50.8)
Nondepressed individuals	8.2 (7.1, 9.6)
Prevalence of having at least one emergency department visit (%)	
Depressed individuals	25.4 (20.7, 29.3)
Nondepressed individuals	26.7 (25.5, 27.8)
Prevalence of having at least one outpatient visit (%)	
Depressed individuals	47.6 (44.0, 50.2)
Nondepressed individuals	30.9 (28.8, 32.6)
Prevalence of having at least one hospitalization (%)	
Depressed individuals	7.7 (5.1, 9.5)
Nondepressed individuals	4.0 (3.4, 4.4)

a. 95% credible intervals

## 9 References

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