A System Dynamics Model to Scrutinize Underlying Reasons for Poor Prescription Adherence

(Case Study: Antibiotic Consumption)

Mehdi Moghadam Manesh
moghadam_manesh@yahoo.com

Khadijeh Salimi
ksali001@odu.edu

1. Introduction and Problem Definition

In 2016, an estimated 41 million deaths occurred worldwide due to noncommunicable diseases (NCDs), accounting for 71% of the overall total of 57 million deaths. The majority of such deaths were caused by the four main NCDs, namely: *cardiovascular disease* (17.9 million deaths; accounting for 44% of all NCD deaths); *cancer* (9.0 million deaths; 22%); *chronic respiratory disease* (3.8 million deaths; 9%); and *diabetes* (1.6 million deaths; 4%) [1]. On the other hand, regarding expenditures, national health spending growth is expected to average 5.5 percent per year for 2017–26 and to reach $5.7 trillion by 2026 [2].

Despite the fact that high adherence is crucial to ensure that medications are effective, adherence rates are low [3]. Wide-scoping cost variations were reported, with lower levels of adherence generally associated with higher total costs. The annual adjusted disease-specific economic cost of non-adherence per person ranged from $949 to $44190 (in 2015 US$). Costs attributed to 'all causes' non-adherence ranged from $5271 to $52341. Medication possession ratio was the metric most used to calculate patient adherence, with varying cut-off points defining nonadherence. The main indicators used to measure the cost of non-adherence were total cost or total healthcare cost (83% of studies), pharmacy costs (70%), inpatient costs (46%), outpatient costs (50%), emergency department visit costs (27%), medical costs (29%) and hospitalization costs (18%) [4]. This makes nonadherence to medications one of the largest and most expensive disease categories.

Moreover, patient nonadherence is not limited to medications alone. It can also take many other forms; these include the failure to keep appointments, to follow the recommended dietary or other lifestyle changes, and to follow other aspects of treatment or recommended preventive health practices. Hence, the actual implications of nonadherence go far beyond the financial aspect of medication nonadherence, as estimated above [5]. Motivational interviewing and cognitive behavioral interventions have been found to individually promote medication adherence. However, there is a gap in the literature on the effect of combined motivational interviewing and cognitive behavioral approaches to promote medication adherence [6].

Patients may consciously decide to modify or discontinue their treatment (intentional non-adherence) because of side effects, lack of understanding of how the treatment works, their beliefs regarding the necessity of the treatment, and other related concerns. They can also become non-adherent because of factors beyond their control (unintentional non-adherence), such as the inability to access the medication (e.g. medication unavailable at the local pharmacy), unclear communication with the physician, misunderstanding of the regimen,3,8 or deficiencies in their memory or dexterity. Patients can be

nonadherent intentionally and unintentionally to the same medication regimen at different times, and both types of non-adherence can overlap as, for example, people with lower motivation to take their medications are less likely to put effort into developing a reliable remembering strategy and therefore are more likely to forget [3]. As an example, in Figure 1 the drop-off in compliance is depicted [7]:

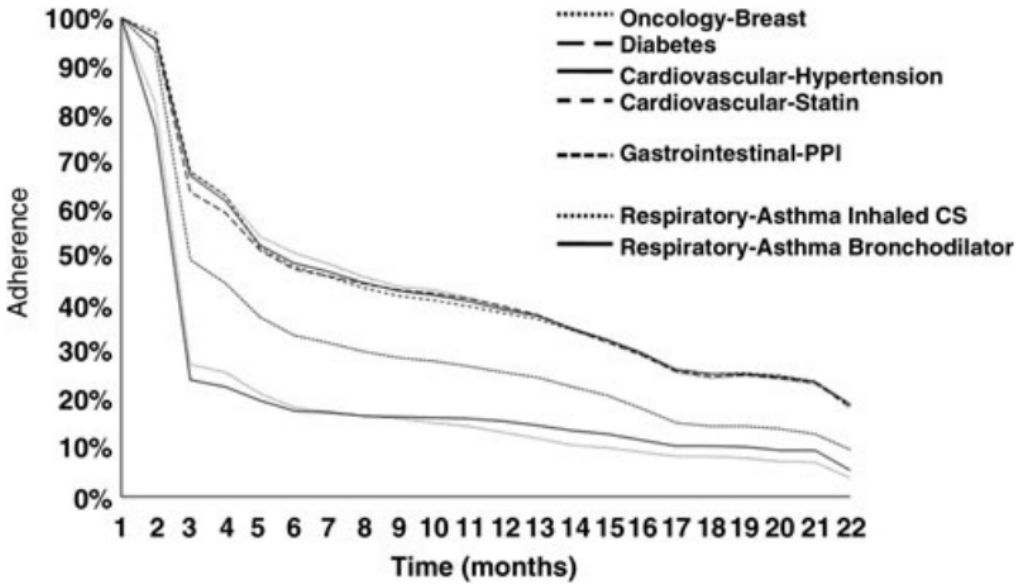


Figure 1: Patient adherence over time for various drug products (Source of data: NDC Health)

Other studies reveal that many patients stop taking their medication, and adherence rates plummet, in just a few months, with 50% to 90% of patients stopping their prescribed therapies by the end of the first year of treatment (see Figure 2) [8]:

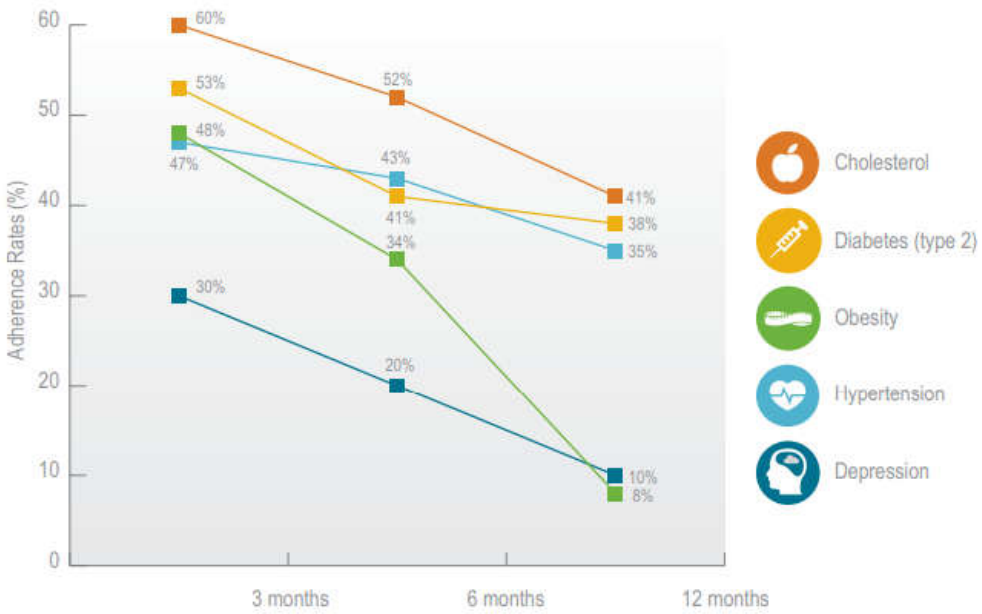


Figure 2: Plummeting Adherence Levels Across Therapeutic Areas Over Time

In this research we intend to apply system dynamics to achieve more insight into the combined effects and underlying structure (mechanisms) of poor prescription adherence in the USA (focusing on the case of antibiotics).

The research questions are: (1) which factors, related to patient characteristics, social resources, and clinical diagnoses, are associated with prescription adherence (case of antibiotics) in the USA? (2) How are the factors, associated with prescription adherence (case of antibiotics) in the USA, dynamically interconnected?

The paper is organized as follows. First we review the literature. Then, assumptions of the model are explained and some related concepts are defined. After that, the model is described. In the end, the results are presented.

2. Literature Review

Literature review reveals that no research has done in this regard, and this study (to the best of our knowledge) is the first step to bridge this theoretical gap. In Table.1, 16 reasons for poor medicine adherence mentioned in the literature are listed, which can be categorized into two groups: "intentional reasons" and "unintentional reasons".

Intentional	unintentional
1. side effects 2. their beliefs regarding the necessity of the treatment 3. Lack of ***trust*** to treatment/ doctor 4. Lack of health insurance 5. Medication cost 6. Duration of therapy	1. forgetting 2. unclear communication with the health practitioner 3. misunderstanding the regimen 4. deficiencies in memory or dexterity 5. inability to access the medication 6. limited language proficiency 7. low health literacy 8. unstable living conditions/ homelessness 9. the complexity of the medication 10. knowledge disease

Table 1: Classification of reasons for poor medicine adherence

3. Assumptions

1) This research will focus on an infectious disease which needs antibiotic consumption
2) The focus of the research will be on "**intentional**" reasons (not "unintentional" ones), & patients may do not take medicine based on a prescription for these reasons:
   a. if they are dissatisfied with effects of medicines, they will change the dosage or time interval
   b. based on cost-benefit analysis or owing to risk management, patients may decide to stop taking the medicine [12]

4. Definition of Concepts

a. Medication adherence: usually refers to patients' ability to conform to a provider's recommendation concerning timing, dosage, and frequency of taking their medications as prescribed [10]
b. Medication Non-adherence/Non -Compliance: is the number of doses not taken or taken incorrectly that jeopardizes the patient's therapeutic outcome [10]
c. Intentional and unintentional non-adherence: patients may consciously decide to modify or discontinue their treatment (intentional non-adherence), or they can become nonadherent because of factors beyond their control (unintentional non-adherence). Intentional non-adherence is often caused by the avoidance of side effects, people's beliefs, and medication-related concerns. Unintentional non-adherence can be caused by the inability to access medications (e.g., they are unavailable at the local pharmacy), unclear communication with the health practitioner, misunderstanding the regimen, or deficiencies in memory or dexterity. [11]
d. Adherence interventions: Several interventions have been devised over the past years to address the problem of nonadherence. However, their effectiveness is questionable. Interventions explicitly addressing forgetfulness are not only a few and far between but also tend to focus on reminders alerting people to take their medications at a specified time, which is in opposition to common remembering strategies described in the previous section. Strategies employed to support the participant's adherence included [11]
    i. reminder systems (dose administration aids, dosette boxes, alarm clock reminders, text reminders, treatment simplification);
    ii. cognitive-educational interventions (pharmacist verbal information, written information);
    iii. reminder systems coupled with cognitive-educational interventions;
    iv. behavioral-counseling interventions (reinforcing behavior, empowering individuals to actively participate in their healthcare and problem-solving) and
    v. social support interventions (family member support)

5. Model Description

I should admit here that the model represented in the following is based on the author's observation and mental model. It goes without saying that reviewing the literature in the future will help us to improve and modify this model.

The model consists of three reinforcing and seven balancing loops, as shown in figure 3

- **R1**: When one gets an infectious disease, "***Number of Virus***" starts to increases based on the virus's ***rate of reproducing***. In a way, if anything does not hinder them, they will increase exponentially & will kill patients. (Fig.3)

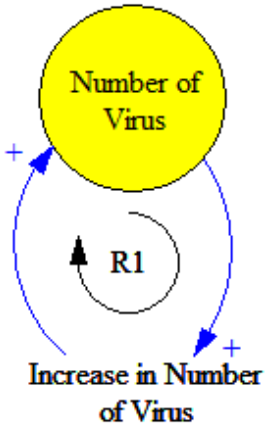


Figure 3: exponential growth of "Number of Virus"

- **R2**: Yet, in normal conditions, the immune system responds to this virus attack by increasing the "**Number of WBC**" (White Blood Cells). "Number of WBC" will increase depending on "***Power of Immune System"*** & "***Number of Virus***." For example, if "***Power of Immune System***" or "***Number of Virus***" is zero, there will be no change in "***Number of WBC***." Nevertheless, the effect of "***Number of Virus***" on "***Number of WBC***" is not specified; sine, on the one hand, increasing "***Number of WBC***" intrigues immune system to produce more WBC, but on the other hand, viruses can kill some WBCs and decrease "***Number of WBC***." As depicted in Fig.4, viruses if have enough time, can attack the immune system and weaken it. This phenomenon creates a second reinforcing loop: the more "***Number of Virus***" the less "***Power of Immune System***," so the less "***Number of WBC***," resulting to the more "***Number of Virus***."

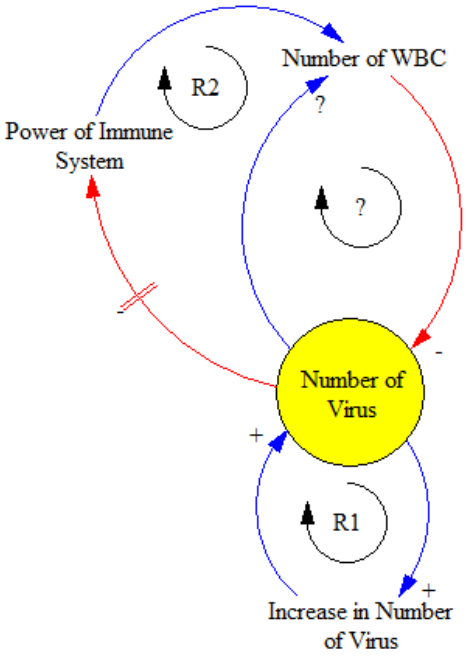


Figure 4: Relationship between "Number of Virus", "Number of WBC", & "Power of Immune System"

- **B1, B2, and B3**: if white blood cells cannot defeat viruses and "***Symptoms***" of diseases increase, "***Perception of Patient about Severity of Disease***" changes, & if patient feels his immune system ("***Perception of Patient about Power of his Immune System***") is not able to beat viruses, "***Feeling Necessity to Take Antibiotic***" increases, so he will visit a doctor & start "***Taking Antibiotic",*** based on prescribed "***Dosage"*** and "***Time Interval***". Consumed antibiotic takes some time to be absorbed by the stomach & enters the blood. "***Antibiotic in Blood***" will decrease by "***Elimination***" creating a balancing loop. "***Effect of Antibiotic on Viruses,"*** besides the amount of "***Antibiotic in Blood***," depends on "***Resistance of Virus to Antibiotic***"; the more resistant are viruses, the less effective will be antibiotics. These relationships between the variables create three more balancing loops: (Fig.5)

  - B1: the more "***Number of Virus***," the more "***Symptoms***," the more "***Feeling Necessity to Take Antibiotic***", the more "***Taking Antibiotic***" (number of days of consuming antibiotic), the more "***Antibiotic in Blood***", so less "***Number of Virus***".
  - B2: the more "***Antibiotic in Blood***", the more "***Elimination***", & the more "***Elimination***" causes the less "***Antibiotic in Blood***"
  - B3: the more "***Number of Virus***", the less "***Power of Immune system***" after a while, so the more "***Feeling Necessity to Take Antibiotic***", which means the more (number of days) "***Taking Antibiotic***", leading to the less "***Number of Virus***"

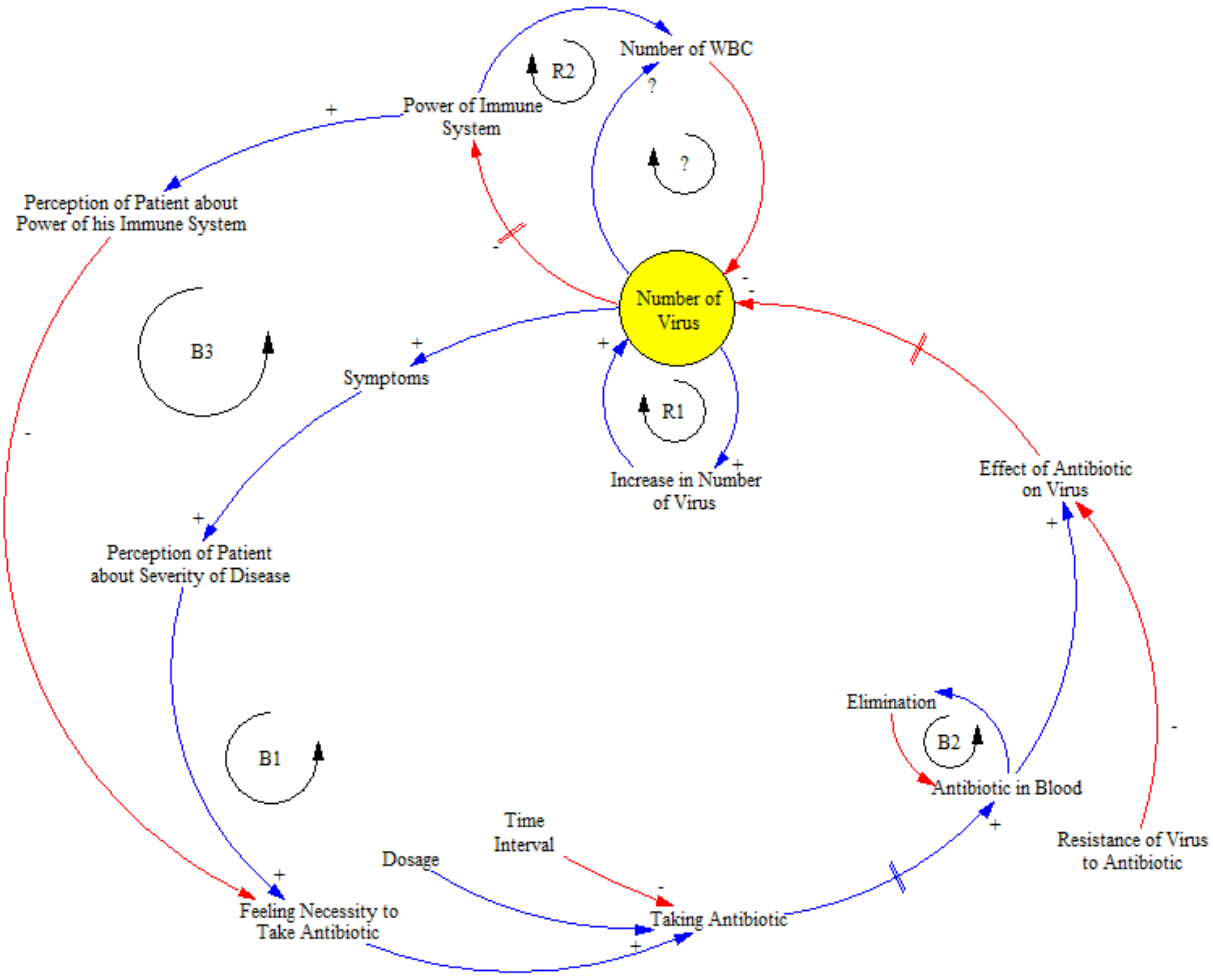


Figure 5: Taking Antibiotic

Another point which should be considered is that "***Effect of Antibiotic"*** on "***Number of Viruses***" & consequently on "***Symptoms***" is not instantaneous, but takes time. This delay & also the absorption delay in the stomach, in turn, can affect the patient's behavior. To clarify, patients has some expectations regarding "trend of improvement" & "duration of illness", but if after "***Taking Antibiotic***", there is a gap between actual "***Symptoms***" & patient's "***Expectation about Medicine Effects***", he will start increasing "***Dosage***" or decreasing & "***Time Interval***".

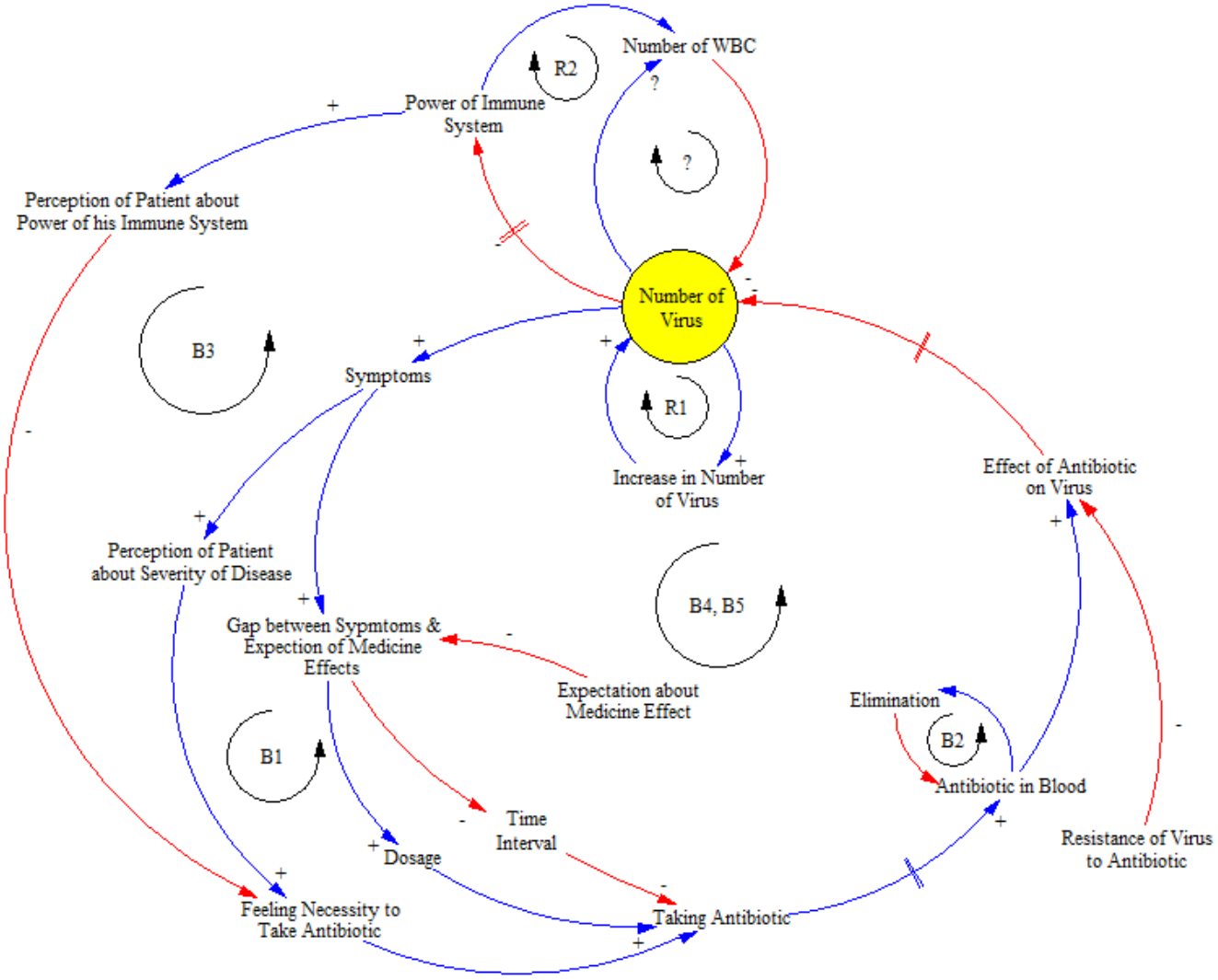


Figure 6: Changing "Dosage" & "Time Interval"

- **B4, B5**: the more "***Gap between Symptoms & Expectation***", the more increase in "***Dosage***" or decrease in "***Time Interval***", so the more "***Taking Antibiotic***", the less "***Number of Virus***", as a result the less "***Symptoms***" & less "***Gap between Symptoms & Expectation***".
- **R3, B6, & B7**: Until now, the side effects of antibiotics are not considered. "***Taking Antibiotic***" & "***Total Antibiotic Usage***" gradually over the time case increase in "***Resistance of Viruses to Antibiotic***", & accordingly decrease in "***Effect of Antibiotic on Viruses***". Moreover, "***Taking Antibiotic"*** is accompanied with some "***Short***

Term Side Effects" such as stomach pain & nausea. Also "***Total Antibiotic Usage***" can increase escalate "***Patient's Fear about Long Term Side Effects***". These costs of "***Taking Antibiotic***" in addition to other costs make patients do a cost-benefit analysis in their minds. Going in depth, in this analysis, "***Perception of Patient about Severity of Disease",*** "***Perception of Patient about Power of his Immune System***", "***Patient's Fear about Long Term Effects***", & "***Sort Term Side Effects***" are considered. If costs outweigh benefits, the patient may not feel "***Necessity to Take Antibiotic***" any longer, and discontinue "***Taking Antibiotic***".

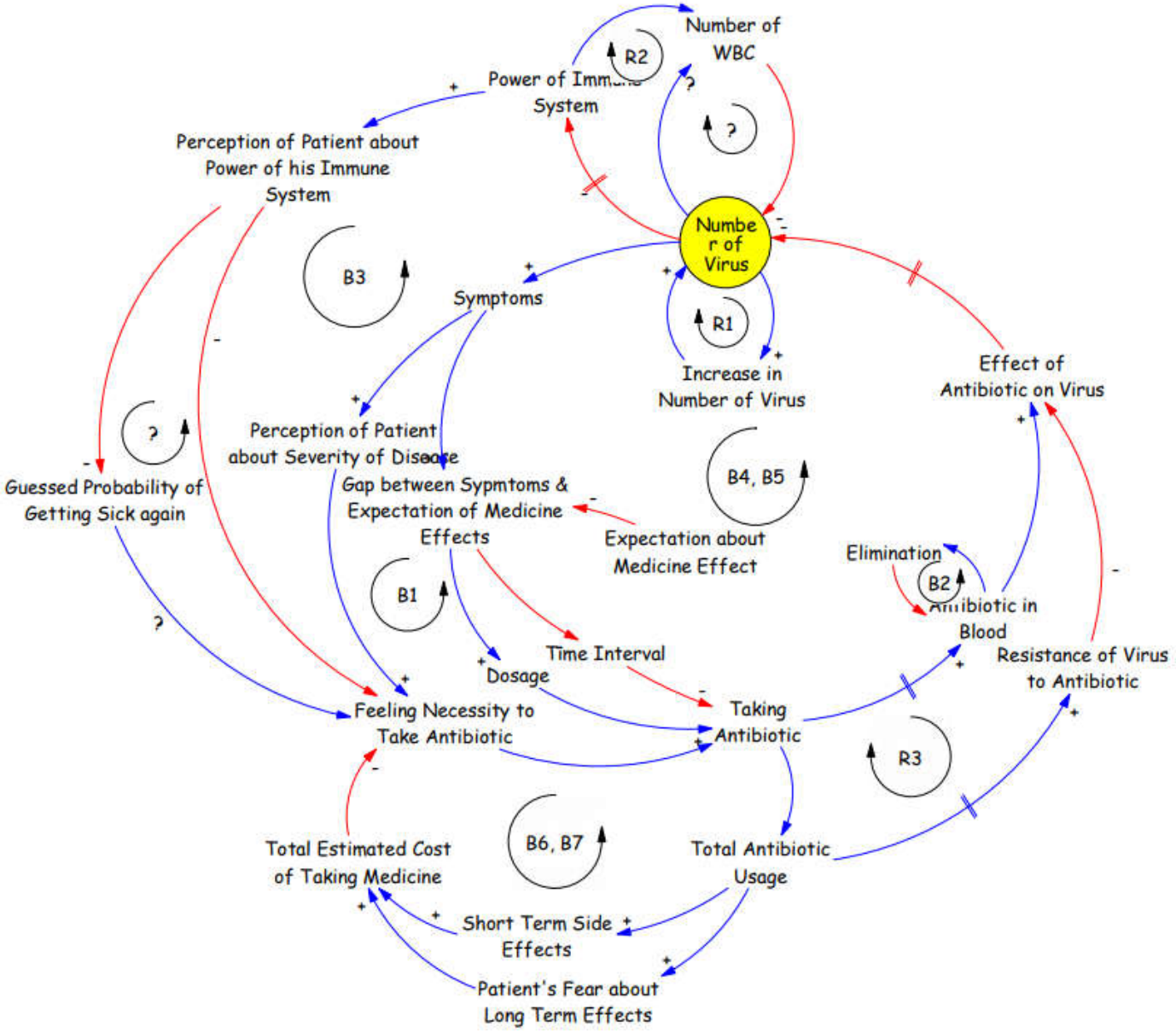


Figure 3: Short & Long Term Side Effects

Albeit, this cost-benefit analysis could encompass more details. For example, after feeling better, patients might discontinue treatment, not due to short-term side effects of fears of long-term side effects, but because of "***Guessed Probability of Getting Sick again***", & the cost of visiting a doctor (financial cost, time cost, & mental costs). So, he may prefer to keep some "***Medicine in Refrigerator***" for risk management. *In fact, everything that*

makes visiting a doctor difficult & bothering can be considered in risk management, e.g. bad behavior of doctors, stress of visiting a doctor, poor accessible medical facilities & having to go another cities to visit a doctor, cost of visiting a doctor, waiting time to book a doctor's appointment, on-site waiting time, …

It should be noted that the relationship between "***Guessed Probability of Getting Sick again***" & feeling necessity to continue "***Taking Antibiotic***" is not very clear. On the one hand, he may think that he will soon again get sick & have to take an antibiotic again, so it is better to discontinue taking antibiotic after relative healing (to minimize side effects of taking antibiotics). On the other hand, he may think that it is better to continue "***Taking Antibiotic***" to postpone next diseases as much as possible (or even continuing "Taking Antibiotic" after complete recovery).

Appendix B: Suggestion for expanding the model

In the model "financial cost", "time cost", & "mental cost" of visiting a doctor are considered exogenous & out of the boundary. Also, some sectors which can affect medicine behavior of people are ignored, for instance, sectors of "Patients", "Doctors", "Insurance Companies", & "Medicine Kept at Home".

1. **Effect of "Power of Immune System" on "Time Spent to Visit a Doctor"**:

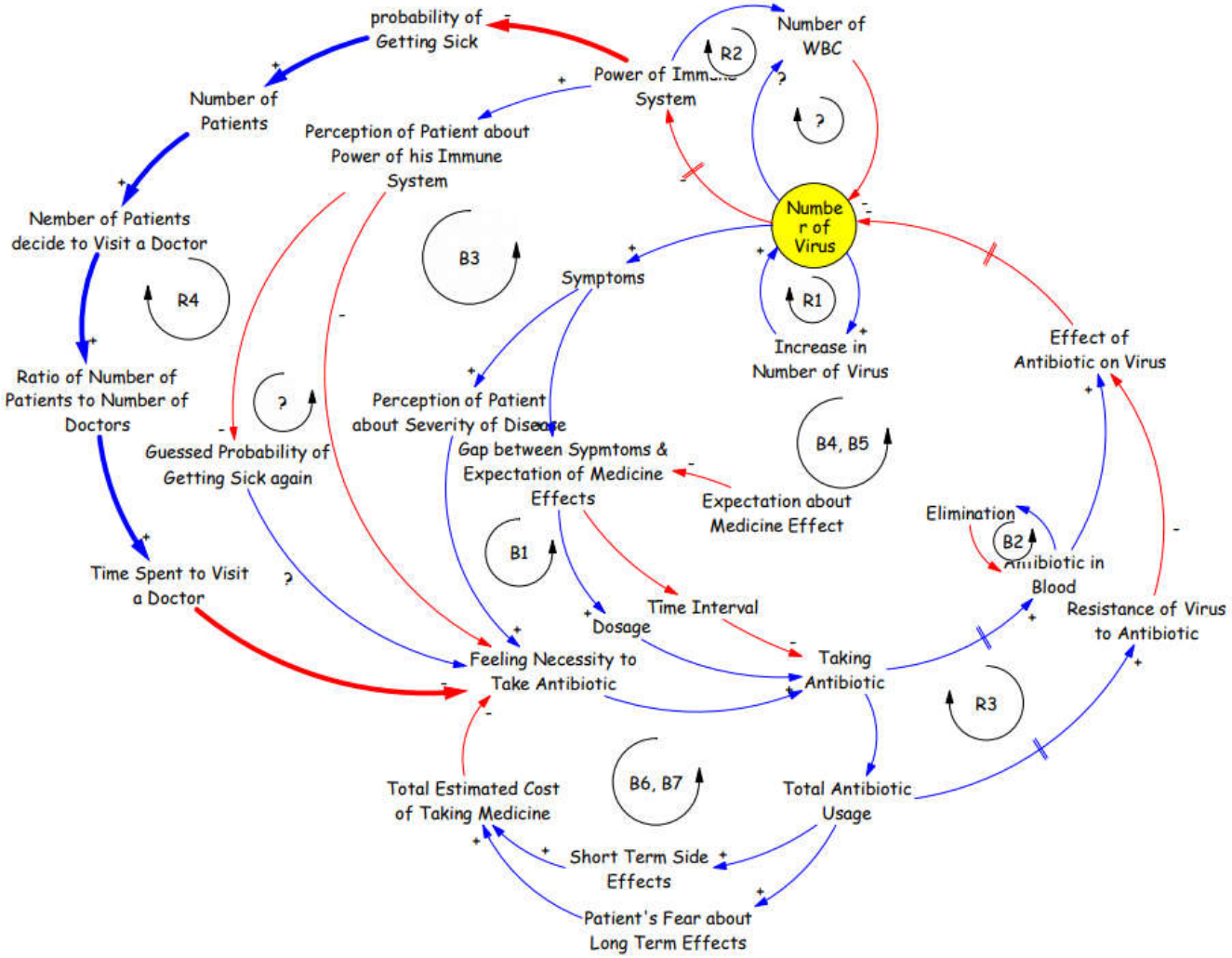


Figure 4: Effect of "Power of Immune System" on "Time Spent to Visit a Doctor"

R4: the less "***Power of Immune System***", the more "***Probability of Getting Sick***", so the more "***Number of Patients***" & "***Number of Patients decide to Visit a Doctor***", as a result, the more "***Ratio of Number of Patients to Number of Doctors***" & the more "***Time Spent to Visit a doctor***". The more time-consuming visit a doctor, the more probability that patients try to keep some medicine in the refrigerator for risk management, which decreases "***Feeling Necessity to Take Antibiotic***" after getting better. The less ""***Feeling Necessity to Take Antibiotic***" causes the less "***Taking Antibiotic***", so the more "***Number of Viruses***", leading to the less "Power of Immune System".

2. **Effect of "Medicine Kept in Refrigerator"**:

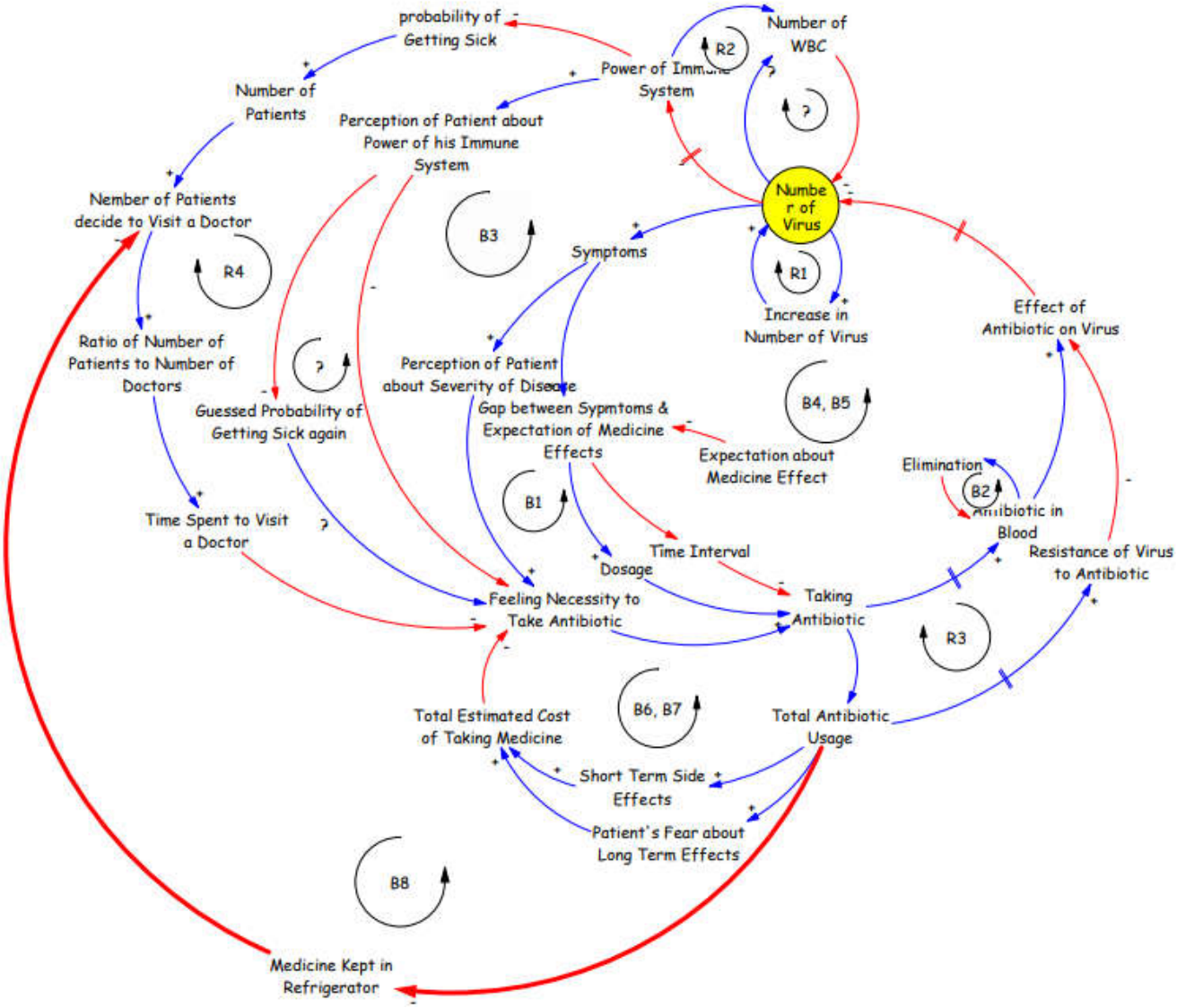


Figure 5: Effect of Medicine Kept in Refrigerator

B8: the more "***Medicine Kept in Refrigerator***", the less probability of visiting a doctor after getting sick, so the less "***Number of Patients decide to Visit a Doctor***", which means the less "***Time Spent to Visit a Doctor***", so the more "***Feeling Necessity to Take Antibiotic***" after getting better, so the more "***Total Antibiotic Usage***".

3. **Including the "Insurance Companies" Sector**:

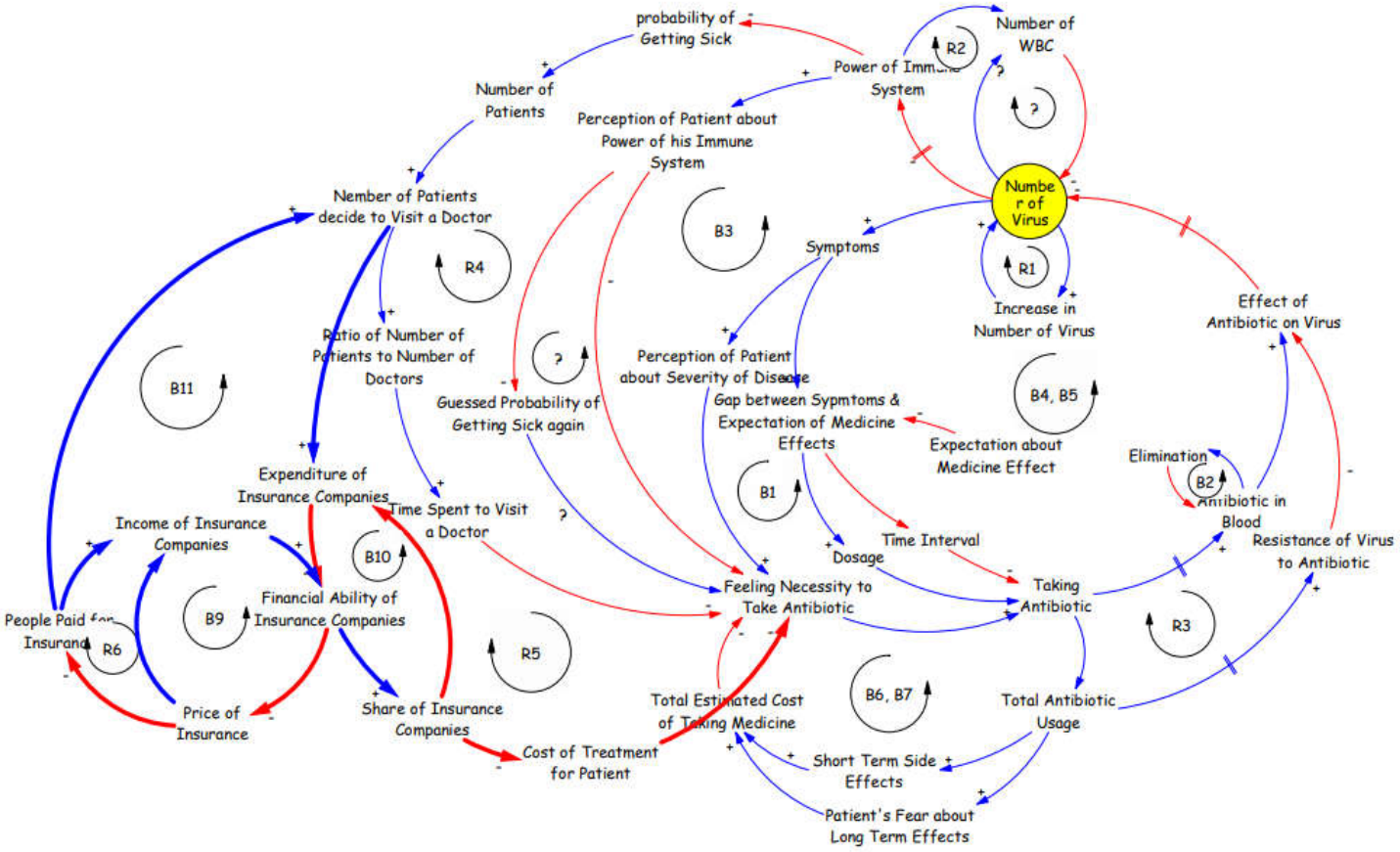


Figure 6: Sector of "Insurance Companies"

As mentioned before, one factor which is considered for risk management is "***financial cost***" of visiting a doctor and buying medicines. "***Cost of Treatment for Patient***" depends on "***Average Cost of Treatment for each Patient***" & "***Share of Insurance Companies***". "***Average Cost of Treatment for each Patient***" will be discussed later. Here, "***Share of Insurance Companies***" is discussed. "***Share of Insurance Companies***" depends on "***Financial Ability of Insurance Companies***"; not surprisingly, the less financial abilities will cause the less share or insurance companies &, the more financial burden will convey to patients' shoulders. "***Financial Ability of Insurance Companies***" is a stock which increases by "***Income of Insurance Companies***" (the multiplication of "***People Paid for Insurance***" & "***Price of Insurance***") , & decreases by "***Expenditure of Insurance Companies***" (multiplication of "***Number of Patients decide to Visit a Doctor***", "***Average Cost of Treatment for each Patient***", & "***Share of Insurance Companies***").

R5: the more "***Number of Patients decide to Visit a Doctor***", the more "***Expenditure of Insurance Companies***", the less "***Financial Ability of Insurance Companies***", so the less "***Share of Insurance Companies***" & the more "***Cost of Treatment for Patients***", resulting the less "***Feeling Necessity to Take Antibiotic***" after getting better, so less "***Taking Antibiotic***", the more "Number of Virus", the more weakening of "***Power of Immune System***", leading to the more "***Probability of Getting Sick***" & "***Number of Patients***", ending to the more "***Number of Patients decide to Visit a Doctor***".

B10: the more "***Share of Insurance Companies***", the more "***Expenditure of Industrial Companies***", the less "***Financial Ability of Insurance Companies***", as a result, the less "***Share of Insurance Companies.***"

B11: the more "***Number of Patients decide to Visit a Doctor***", the more "***Expenditure of Insurance Companies***", the less "***Financial Ability of Insurance Companies***", so trying to increase "***Price of Insurance***", leading to the less "***People Paid for Insurance***", so the less "***Number of Patients decide to Visit a Doctor***" (assuming that having an insurance is an affecting factor that people consider when getting sick & deciding whether visit a doctor or not)

B9: the higher "***Price of Insurance***", the higher "***Income of Insurance Companies***", the more "***Financial Ability of Insurance Companies***", so the lower "***Price of Insurance.***"

R6: the more "***Financial Ability of Insurance Companies***", the lower "***Price of Insurance***", the more "***People paid for Insurance***", the more "***Income of Insurance Companies***", & the more "***Financial Ability of Insurance Companies.***"

4. **Including the "Doctors" Sector**:

Doctors have an "Expected Income", & if there is a "Gap between Actual & Expected Income", they may show four reactions: (1) spending less time for visiting each patient to be able to visit more patient per day (2) asking patients to visit them monthly to monitor the progress of disease & changing medicines (3) making contract with medical laborites & imaging canter, & getting commission for each sent patient (4) making contract with drug stores to prescribe some expensive medicines. These actions can harm "***Trust to Doctors/ Medication***" & increase bother & cost of visiting a doctor which affect medicine adherence of patients.

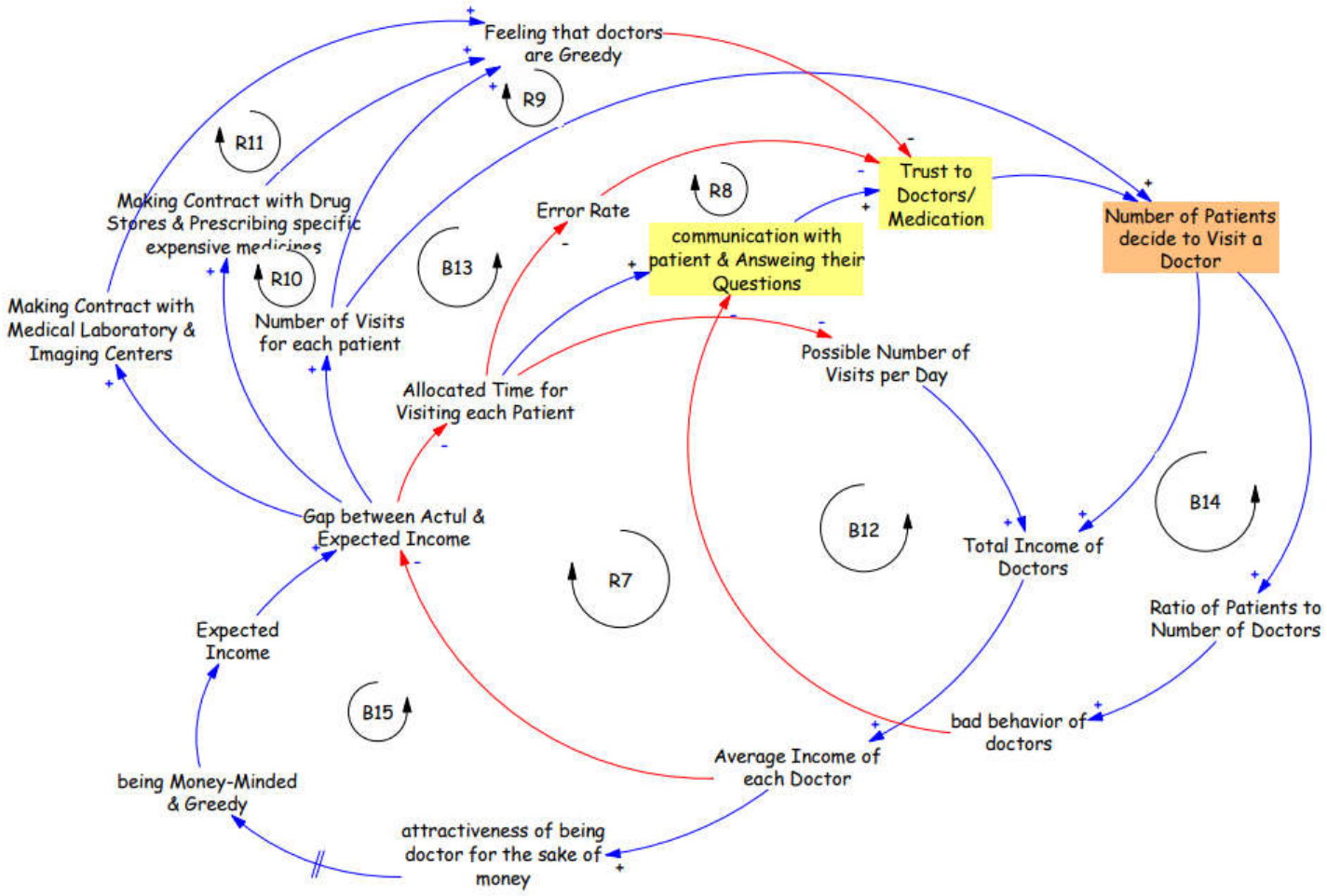


Figure 7: Sector of Doctors

R7: the less "***Number of Patients decide to Visit a Doctor***", the less "***Total Income of Doctors***", the less "***Average Income of each Doctor***", the more "***Gap between Actual & Expected Income***", the less "***Allocated Time for Visiting each Patient***", so the less "***Communication with Patient & Answering their Questions***", leading to the less "***Trust to Doctors/ Medication***" & the less "***Number of Patients decide to Visit a Doctor***".

B12: the less "***Total Income of Doctors***", the less "***Average Income of each Doctors***", the more "***Gap between Actual & Expected Income***", so the less "***Allocated Time for Visiting each Patient***", leading to the more "***Possible Number of Visits per day***", & the more "***Total Income of Doctors***".

R8: the less "***Number of Patients decide to Visit a Doctor***", the less "***Total Income of Doctors***", the less "***Average Income of each Doctor***", the more "***Gap between Actual & Expected Income***", the less "***Allocated Time for Visiting each Patient***", so the more "***Error Rate***", the less "***Trust to Doctors/ Medication***", resulting the less "***Number of Patients decide to Visit a Doctor***"

R9, R10, and R11: the less "***Number of Patients decide to Visit a Doctor***", the less "***Total Income of Doctors***", the less "***Average Income of each Doctor***", the more "***Gap between Actual & Expected Income***", the more ["***Number of Visits for each Patient***" + "***Making Contract with Drug Stores & Prescribing specific expensive medicines***" + "***Making Contract with Medical Laboratory & Imaging Centers***"], leading to the more "***Feeling that Doctors are Greedy***", so the less "***Trust to Doctors/ Medication***", causing the less "***Number of Patients decide to Visit a Doctor***".

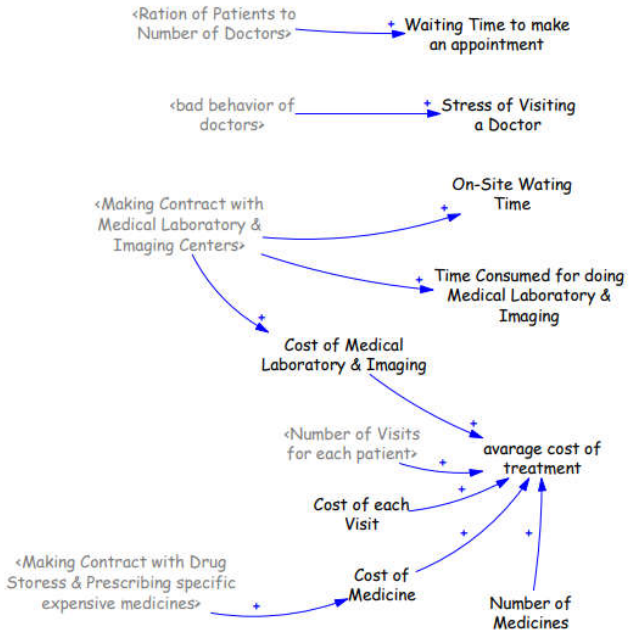
B13: the less "***Number of Patients decide to Visit a Doctor***", the less "***Total Income of Doctors***", the less "***Average Income of each Doctor***", the more "***Gap between Actual & Expected Income***", the more "***Number of Visits for each Patient***", so more "***Number of Patients decide to Visit a Doctor***" (because for each visit, patients have to make a new appointment & pay the cost of doctor's visit)

B14: the more "***Number of Patients decide to Visit a Doctor***", the more "***Ratio of Patients to Number of Doctors***", so the more proud & selfish are doctors & behave arrogantly with people, that is, the more "***bad behavior of Doctors***", causing the less "***Communication with Patients & Answering their Questions***", resulting the less "***Trust to Doctors/ Medication***" & the less "***Number of Patients decide to Visit a Doctor***"

B15: the more "***Average Income of each Doctor***", the more "***attractiveness of being doctor for the sake of Money***", leading to the more "***Money-Minded & Greedy***" people are attracted to medical professions in long run, so the more "***Expected Income***", the more "***Gap between Actual & Expected Income***", …

how the factors mentioned above affect medicine adherence:

1) "***Communication with Patients***" & "***Trust to Doctors/ Medication***" directly influences medicine adherence
2) "***bad behavior of doctors***" increases the mental cost & "***Stress of Visiting a Doctor***," so patients try to save some "***Medicine Kept in Refrigerator***" for risk management
3) The more "***Ratio of Patients to Number of Doctors***," the more "***Waiting Time to make a doctor's appointment***" → bother & difficulty of visiting a doctor → try to have some "***Medicine Kept in Refrigerator***" for risk management
4) Sending patients to medical laboratories & imaging center is not only a lot time-consuming but also money-consuming. Also, since patients do not need to make an appointment to show the images & results of laborites, & doctors visit them between scheduled



patients, it causes more "***On-site Waiting Time***" → bother & difficulty of visiting a doctor → try to have some "***Medicine Kept in Refrigerator***" for risk management

5) "***Prescribing specific expensive medicines***" increases "***Average Cost of Treatment***" → try to have some "***Medicine Kept in Refrigerator***" for risk management
6) Increasing "***Average Cost of Treatment***" causes more financial burden on "***Insurance Companies***" & as mentioned before, the less "***Financial Ability of Insurance Companies***" means the less "***Share of Insurance Companies***" & the more "***Cost of Treatment for Patients***" → try to have some "***Medicine Kept in Refrigerator***" for risk management

5. **Psychological Sector**:

Taking medicine for a long time, sense of being sick & dependent on medicines, sticking to the recommended dietary, etc. are nerve-racking, and people have a certain carrying capacity. This carrying capacity can cause an "S-shaped," "S-shaped growth with overshoot," or "***overshoot & collapse***" behavior. For example, if accumulated mental pressure on the patient erodes patient's carrying capacity over the time, when it passes the carrying capacity happens & patients suddenly stop taking medicine. Also, if carrying capacity is constant, it can cause oscillation behavior; sometimes a patient will be more adherent to medicine & sometimes less adherent.

6. **Aging Chain**:

Aging chain can have an influence on "***Probability of getting Sick***", "***Number of Patients",*** "***Forgiving***" to take medicine, having different chronic diseases & consuming different drugs for each of them which in turn affect "***Complexity of the medications***", & decrease the effect of medicines due to "***Drug Interactions***"

Results

- What are the most effective policies to increase prescription adherence rate (case of antibiotics) in the USA?

Reviewer 1: Very interesting and relevant subject to prescription adherence. Employs causal loop diagramming to present many intriguing speculative relationships and loops. Suggest that a hybrid diagram showing stocks, and some of the key rates of change would help interpretation and provide a stronger pathway to a quantitative model. Hard to believe there is no relevant literature. Tell us more about your search terms and strategy. Where did you get the 16 reasons if there is no literature? Did you create this list? How? Why did you select antibiotics? They are mostly and intentionally prescribed to be taken in a 7-14 days and then stopped. So why not study medications for chronic disease? The sequential additions of complex layers eventually became too much. Might be best to move the simpler core CLD to a quantitative formulation and build on that.

(Only to Author): page 1, middle: "wide-scoping" does this mean wide variety?

page 4, middle: you mention "previous section" what section, the assumptions section?

lower on page, you mention reviewing the literature in the future, but earlier you said there was no relevant literature confusing

Figure 4: seems to me the ? loop is a B loop

lots of interesting ideas, but might have taken CLD thinking farther than useful

Reviewer 2: This paper provides several CLDs to describe the system(s) at play for poor medication adherence within the context of taking antibiotics. It presents several parts of the system informed by the literature and the authors' mental model. Additional analysis of the literature, understanding of the issues at play, and perhaps some data collection or validation from providers and patients would be helpful.

(Only to Author): 1. Good abstract! Abstracts aren't usually indented.

2. References aren't consistently formatted.

3. References from 2019, 2020, 2021 would be useful.

4. Additional references (quantity) would be useful.

5. Good definition of concepts.

6. Good that you described all the loops. See if there is a way you can make it more engaging when you describe them or if there is a standard way of doing this in the literature.

7. You use antibiotics as a case study but then provide a literature review on prescription medication adherence more broadly. I think there might be a difference here as to whether people take antibiotics vs. whether they take their prescription for a chronic condition. I suggest exploring this a bit further and providing a literature review based on the question you're really asking.

8. I suggest unpacking "feeling necessity to take antibiotic" a bit further.

9. There seems to be some inconsistent font type or size throughout.

10. What is informing your goal-gap analysis of the doctors?

11. What system is this and where is it located? Is this a US system? A European system?

12. Are there any systems archetypes you could draw from here?

13. Antibiotics are not effective on viruses. Only on bacteria.

14. Physicians aren't the only ones who can prescribe antibiotics. I suggest using the term "providers" instead.

Reviewer 3: It is not accurate to say that this is a “System Dynamics Model.” It is a proposed causal loop diagram to guide investigations into prescription adherence. The diagrams need support from the literature or evidence or both. The paper shows that that the author has some facility constructing CLDs. The work is incomplete.

(Only to Author): It is my pleasure to review this paper. It is not accurate to say that this paper is a “System Dynamics Model.” It is a proposed causal loop diagram to guide investigations into prescription adherence. Poor prescription adherence is similar to other behavioral problems, such as failure to quit smoking, lose weight or save money; as well as to larger societal issues, like failure to address gun violence or climate change. There is significant literature on why people do not do things that would make the more healthy, wealthy, or their planet more sustainable. I suggest investigating the literature on issues like smoking, or on NCDs such as cardiovascular disease or diabetes.

The problem asks why it is difficult to change a behavioral or societal “set point.” The outward appearance is that negative feedbacks are sufficiently strong and delays sufficiently long that they return the system to the previous operating point even in the face of external pressures or disturbances.

1. Introduction and Problem Definition

Although the case study is “Antibiotic Consumption,” paragraph one leads with a discussion of NCDs, which is not applicable to diseases treated by antibiotics.

2. Literature Review

The paper should be supported by a complete literature review. Regarding “Intentional/Unintentional,” the divisions are not helpful. Surely side effects or high medication costs are not intentional. Maybe a different division of “reasons” would help.

External (not related to behavior): cost, side effects, complexity of dosing, duration of therapy, lack of health insurance, deficiencies in memory or dexterity, language barriers, unclear communication.

Internal (behavioral): beliefs, lack of trust, forgetting, incomplete knowledge.

5. Model Description

I find the emphasis on “Infections Disease” to be confusing. I think a focus on a NCD such as diabetes would be more illuminating. I expect that there is significant literature on this.

I am confused by the figures. At the top on one (unnumbered) page, there is this: "In the model, 'financial cost', time cost', & 'mental cost' ... are considered exogenous", and then in figures 4, 5 and 6, cost is included. This raises a question regarding the value of model that includes only behavioral factors, when a not-behavioral factor such as cost may have the largest influence on non-adherence.

Suggestions:

1. Conduct an exhaustive literature search on related health issues, focusing on NCDs.
2. Focus the CLD on externals (not related to behavior) factors.
3. Find related time-series data.
4. Build a simple stock and flow model.

I hope this helps.

References

[1] World health statistics 2018: monitoring health for the SDGs, sustainable development goals. ISBN 978-92-4-156558-5

[2] Cuckler GA et al. 2018. National Health Expenditure Projections, 2017-26: Despite Uncertainty, Fundamentals Primarily Drive Spending Growth. Health Aff (Millwood). 2018 Mar;37(3):482-492. doi: 10.1377/hlthaff.2017.1655. Epub 2018 Feb 14

[3] Stawarz, K.M., Rodríguez, M.D, Cox, A.L. & Blandford, A. 2016. Understanding the role of contextual cues: Design implications for medication adherence technologies that support remembering. Digital Health, 2:1-18

[4] Rachelle Louise Cutler et al. 2018. Economic impact of medication non-adherence by disease groups: a systematic review. BMJ Open. 2018; 8(1): e016982

[5] Ashish Atreja, et al. 2005. Strategies to Enhance Patient Adherence: Making it Simple. MedGenMed. 2005 Mar 16;7(1):4

[6] Sandra L. Spoelstra et al. 2014. Interventions combining motivational interviewing and cognitive behaviour to promote medication adherence: a literature review. Journal of Clinical Nursing, 24, 1163–1173, doi: 10.1111/jocn.12738

[7] Ian J. Smith, et al. 2010. Inhaler Devices: What Remains to be Done?. JOURNAL OF AEROSOL MEDICINE AND PULMONARY DRUG DELIVERY Volume 23, Supplement 2, 2010

[8] Srivatsan N et al. 2014. Medication adherence in the real world. Cognizant 20-20 Insights: October 2014

[9] Thi-My-Uyen Nguyen. 2015. Improving medication adherence in patients with chronic disease using a targeted and tailored approach. A thesis submitted for the degree of Doctor of Philosophy at The University of Queensland in 2015 School of Pharmacy

[10] P. Michael Ho, Chris L. Bryson, John S. Rumsfeld. 2009. Medication Adherence Its Importance in Cardiovascular Outcomes. **Circulation. 2009;119:3028-3035**

[11] Katarzyna M. Stawarz. 2017. Towards better medication adherence apps: Preventing forgetfulness by facilitating the formation of routine-based remembering strategies. **PhD thesis, University College London**

[12] Leventhal, Howard; Phillips, L Alison; Burns, Edith. (2016). The Common-Sense Model of Self-Regulation (CSM): a dynamic framework for understanding illness self-management .Journal of Behavioral Medicine; New York Vol. 39, Iss. 6, (Dec 2016): 935-946. DOI:10.1007/s10865-016-9782-2

Lofland JH, et al. 2017. Shared decision-making for biologic treatment of autoimmune disease: influence on adherence, persistence, satisfaction, and health care costs. **Patient Prefer Adherence 2017;11:947–58**

[13] Hilliard ME, Ramey C, Rohan JM, Drotar D & Cortina S . 2011. Electronic monitoring feedback to promote adherence in an adolescent with Fanconi anemia. **Health Psychology 30, 503–509**

[14] Hon, A . 2012. Factors influencing the adherence of antipsychotic medication (Aripiprazole) in first-episode psychosis: Findings from a grounded theory study. **Journal of Psychiatric and Mental Health Nursing, 19(4), 354–361**

[15] Eticha T, Teklu A, Ali D, Solomon G, Alemayehu A. 2015. Factors Associated with Medication Adherence among Patients with Schizophrenia in Mekelle, Northern Ethiopia. **PLoS ONE 10(3): e0120560. doi:10.1371/journal. pone.0120560**

[16] E. Vermeire et al. 2001. Patient adherence to treatment: three decades of research. A comprehensive review. **Journal of Clinical Pharmacy and Therapeutics (2001) 26, 331±342**

[17] Keren Ladin et al. 2018. Is social support associated with post-transplant medication adherence and outcomes? A systematic review and meta-analysis. **Transplantation Reviews 32 (2018) 16–28**

[18] Donald Edmondson et al. 2018. A systematic review of the inclusion of mechanisms of action in NIH-funded intervention trials to improve medication adherence. **Behaviour Research and Therapy 101 (2018) 12–19**

[19] Jack Homer, et al. 2001. Toward a dynamic theory of antibiotic resistance. System Dynamics Review. 26 January 2001

[20] J. M. Vanrossum;J. E. G. M. Debie. 1990. System Dynamics and Chaos Theory in Drug Action. European Journal of Pharmacology

[21] Amitava Dutta;Rahul Roy. 2008. Dynamics of organizational information security. System Dynamics Review

[22] Wayne Wakeland, et al. 2011. System Dynamics Modeling as a Potentially Useful Tool in Analyzing Mitigation Strategies to Reduce Overdose Deaths Associated with Pharmaceutical Opioid Treatment of Chronic Pain, *Pain Medicine, Volume 12, Issue suppl_2, 1 June 2011, Pages S49–S58*

[23] T.D. Wickens. 1993. Quantitative Methods for Estimating the Size of a Drug-Using Population. Journal of Drug Issues

[24] Nabil Mikati. 2010. Simulating the spread of resistance to antibiotics. Proceedings of the 28th International Conference of the System Dynamics Society

[25] James Rogers, et al. 2011. Individualized Medicine and Biophysical System Dynamics: An Example from Clinical Practice in End Stage Renal Disease. Proceedings of the 29th International Conference of the System Dynamics

[26] Jose J. Gonzalez;Agata Sawicka. 2003. The Role of Learning and Risk Perception in Compliance Robert. Proceedings of the 21st International Conference of the System Dynamics Society

[27] Jiyang Lee;Qifan Wang. 1987. Applying System Dynamics to the Study of Pharmacokinetics and Pharmacodynamics. Proceedings of the 1987 International System Dynamics Conference

[28] Rita Hattemer-Apostel;Martin Simon. 2003. Dynamic Process Management towards Sustained Compliance and Benefit in Clinical Research. Proceedings of the 21st International Conference of the System Dynamics Society

[29] Barlas Y. 1996. Formal aspects of model validity and validation in system dynamics. **System Dynamics Review 12(3): 183–210**.

[30] Richardson, G.P. (2011): Reflections on the Foundations of System Dynamics. **System Dynamics Review 27, 219–243**.

[31] Vennix, J. A. M. (1996). Group model building : facilitating team learning using system dynamics. **Chichester ;: J. Wiley**.

[32] De Gooyert, V. (2018) Developing dynamic organizational theories; three system dynamics based research strategies. **Quality & Quantity (online)** https://doi.org/10.1007/s11135-018-0781-y [accessed 21-01-2019].

[33] Academy of Management Journal. 2011. Academy of Management Journal; Style guide for authors. **Academy of Management Journal, 54: 1081-1084**.

[34] Turner, B. L., Kim, H., & Andersen, D. F. 2014. Improving coding procedures for purposive text data: researchable questions for qualitative system dynamics modeling. **System Dynamics Review, 29: 253-263**.

[35] Andersen, D. L., Luna-Reyes, L. F., Diker, V. G., Black, L., Rich, E., & Andersen, D. F. 2012. The disconfirmatory interview as a strategy for the assessment of system dynamics models. **System Dynamics Review, 28: 255-275**.

[36] Barlas Y. 1989. Multiple tests for validation of system dynamics type of simulation models. **European Journal of Operational Research 42(l), 59-87**

[37] Barlas Y. 1990. An autocorrelation function-test for output validation. **Simulation 55(l), 7-16**