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Virtual Clinical Trials: A tool for the Study of Transmission of Nosocomial Infections

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Abstract

A clinical trial is a study designed to demonstrate the efficacy and safety of a drug, procedure, medical device, or diagnostic test. Since clinical trials involve research in humans, they must be carefully designed and must comply strictly with a set of ethical conditions. Logistical disadvantages, ethical constraints, costs and high execution times could have a negative impact on the execution of the clinical trial. This article proposes the use of a simulation tool, the MRSA-T-Simulator, to design and perform "virtual clinical trials" for the purpose of studying MRSA contact transmission among hospitalized patients. The main advantage of the simulator is its flexibility when it comes to configuring the patient population, healthcare staff and the simulation environment.

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Keywords: Simulation, Agent Based Model, Clinical Trials, Nosocomial Infection

1 Introduction

In the medical field, the transmission of Nosocomial Infection (NI), which is an infection acquired within hospital settings, is a widely studied phenomenon. According to data published by the European Center for Disease Prevention and Control [21], about 7.1% of hospital patient acquire at least one NI during their stay. There are several hospital microorganisms which are capable of producing a nosocomial infection, but we will focus on Methicillin-resistant Staphylococcus Aureus (MRSA) [4]. Since MRSA is transmitted by physical contact, the frequent interaction between patients and Healthcare Workers (HCWs) or the hospital environment, and long length of stays all increase the transmission risk of MRSA. To minimize the percentage of patients who acquire NI several actions such as washing and disinfecting hands and the use of isolation material are performed by HCWs. We called these actions Infection Control Measures (ICM). The application of the ICM has an impact on the rate of propagation, as many studies published

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in this line demonstrate [20][15] [5]. However, it is very difficult to quantify the importance of compliance with ICM or to know what would happen if we stop applying them.
One of the mechanisms used to assess the efficacy of some medical procedures on transmission rates are the Clinical Trials (CTs). The World Health Organization defines the CT as "Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include, but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc."[13]. CTs should be based on a protocol or plan of action which describes what is done in the study, how it is done and why each part of the study is necessary. All of these characteristics define who participates in the CT (inclusion criteria: age, sex, presence of a particular disease, among others). At times, it is not easy to ensure that the population studied meets all the necessary characteristics, affecting both the quality of the results obtained and the increased time and costs of conducting the CT. Moreover, CTs are always subject to the approval of an ethics committee, which seeks to ensure that the study is ethical and the well-being of the participants is protected at all times. In other words, in a real CT there will be certain situations that cannot be considered because these are dangerous for patients.
This article proposes the use of a simulation tool, the MRSA-T-Simulator, to design and perform " Virtual Clinical Trials" (VCTs) for the purpose of studying MRSA contact transmission among hospitalized patients. The VCT could be a cost-effective alternative in situations where, due to ethical, economic or time limitations, it was difficult to design and implement a CT. The validity of the simulation results would not be comparable to a real CT, but could offer relevant information in those situations in which the CT cannot be performed or as a pre-implementation situation.
The simulation began to be used in the 1970s as a tool for the solution of problems related to the healthcare field. Issues such as the improvement in the planning of the configuration of HCWs, the influence of the lengh of stay of patients in the hospital system, the optimization of resources, or the transmission of diseases acquired in the healthcare environment have been widely studied through the application of different techniques. Some simulations used mathematical models to simulate aspects such as studying the impact of infection control programs on the spread of MRSA [16], or to studying the transmission dynamics of MRSA [18][2]. Another simulation technique is the Agent Based Model and Simulation (ABMS). This approach has the advantage that it provides more flexibility when we need represent stochastic processes. There are several studies that apply ABMS models to study MRSA transmission. For instance, in [11] an agent-based simulation to determine how the problem might be managed and the risk of transmission reduced is developed. Another study [12] showed an individual-based model and simulator to investigate MRSA outbreaks in a hospital ward. Additionally, ABMS approach has been used to provide information to support decisions makers to healthcare services[8].
Simulation techniques have also been used to design CTs with different approaches. They can help refine dose selection [1] [9] and study design, and to represent dose-response and time-response behaviour of safety and efficacy endpoints [14]. Some studies use preclinical data to construct simulation models and to provide prior information on model parameters. Thus, the results from a proof-of-concept study can be used to study a similar model to be used in a subsequent study [19] [7].
As we can see, the use of simulation in the field of healthcare has multiple applications. From its use as a tool to make decisions at the managerial level, to the development of simulations of CTs related to the design of drugs and other applications. In our case, the main objective is to show that a real CT can be replicated through the use of an ABMS simulation tool through

the appropriate parameterization of said tool. The ultimate goal is not to "replace" the real CT, but to complement it, arriving through simulation, where the actual CT cannot arrive. The remainder of this article is organized as follows: In Section 2, some fundamental concepts about CTs and our simulation tool are briefly reviewed. The process followed to desing VCTs is explained in Section 3. Section 4 details some experimental results, and finally, Section 5 closes this paper with conclusions and future work.

2 Previous concepts

2.1 Clinical Trial: Definition and Characteristics

As mentioned above, a CT is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes[13]. All CTs are designed to answer a clinical problem or gain a new knowledge. Since a CT is a study that involve humans, this is a carefully designed process. For a better understanding, we have summarized the whole process in four steps: (1). The initial step is the definition of the study objective. This objective will allow the approach of the hypothesis that will be accepted or rejected at the end of the study. (2). Based on this hypothesis the researchers will define the specific questions to be answered, which will determine other details of the research such as the inclusion and exclusion criteria for study participants, the type of CT (crossover, blind, double blind), the variables to be measured, the input data and what variables to be considered as the output data are. (3). The next step is the implementation of the study. Participants are selected on the basis of the inclusion criteria defined and their consent to participate in the study is obtained. Then the samples and input data that the study requires are taken (4). Finally, specialized personnel are responsible for the analysis of the samples and the measurement and calculation of the output data (Fig. 1).

It is worth noting that patients who participate in a CT are volunteers. Also, it should be considered that of the total population of patients, only those who meet the established inclusion criteria will be chosen and only those who have given their consent will form part of the study.

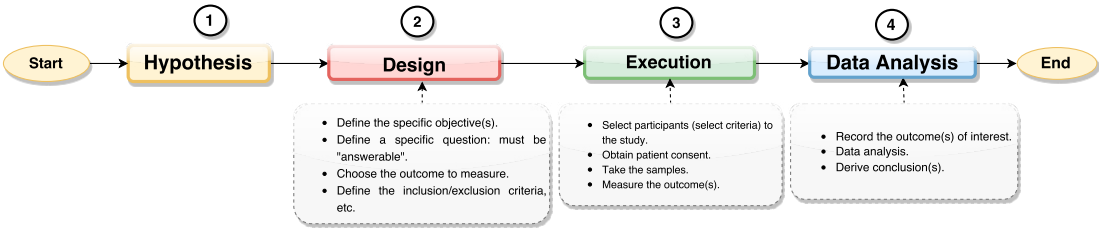


Figure 1: Flow of clinical trial design and execution process

2.2 MRSA-T-Simulator: A tool to design virtual clinical trials

The MRSA-T-Simulator is a simulator of contact transmission of MRSA. This simulator was developed with ABMS techniques[10]. The main feature of MRSA-T-Simulator allows us to analyse the probability of transmission in each of the physical contacts which occur during the process of normal care of a patient in a health service. Thus, we have a layer of health

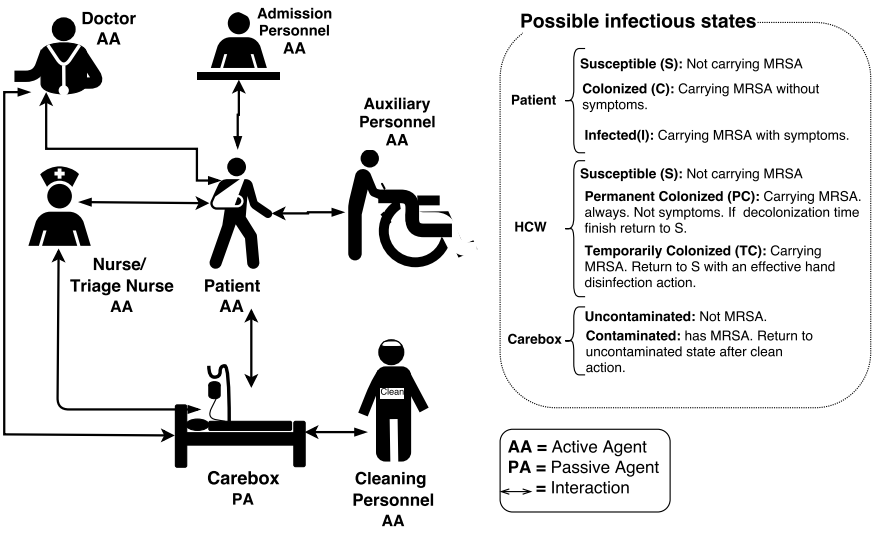


Figure 2: Contacts between agents involve in transmission process.

system operation, where patients, HCWs and environment interact with each other and on added to this, another one, the MRSA transmission layer in which every time a patient comes into contact with an HCW or with the environment, the simulator analyzes if a transmission is possible or not. Of course, the main condition is that one of the agents in contact is carrying MRSA and the other is susceptible to acquire it. The agents are divided into active agents and passive agents. Active agents are all people involve of the care process, patients and HCWs. Passive agents are the objects and equipment of the medical environment and which have been represented in the passive agent carebox (Fig. 2). It is assumed that all transmission event results in a colonization or infection in the case of patients. Both colonization and infection means that patient carrying MRSA, but only in the infection case the patient shows symptoms. For HCWs, it is assumed that all transmission results in a temporary colonization (TC) or permanent colonization(PC). TC means that a HCW carrying MRSA, but it can be eliminated if HCW washes or disinfectes their hands. When an HCW is PC a hand washing or hand disinfection action will not eliminate MRSA bacterium. If the agent who acquired MRSA is the carebox, it is assumed that the carebox is contaminated and it could return to the uncontaminated state only through a disinfection process carried out by the cleaning staff.
For the operation of the simulator, defining two sets of parameters is necessary (Fig. 3). The first set corresponds to the **Environment Configuration Parameters**, and it includes: Input Patient Configuration, Input Ward Facilities Configuration, Input HCW Configuration and Input ICM Configuration. The second set corresponds to the internal variables that models the probability of transmission between one agent who carrying MRSA and another agent susceptible to acquire it. These are the **Internal Transmission Variables** and includes a set of transmission coefficients that depends of who is the agent in risk to acquired MRSA. The values used in each case will described in Section 3.2. A more detailed explanation of the complete MRSA-T-Simulator model can be found in a previous publication[6].

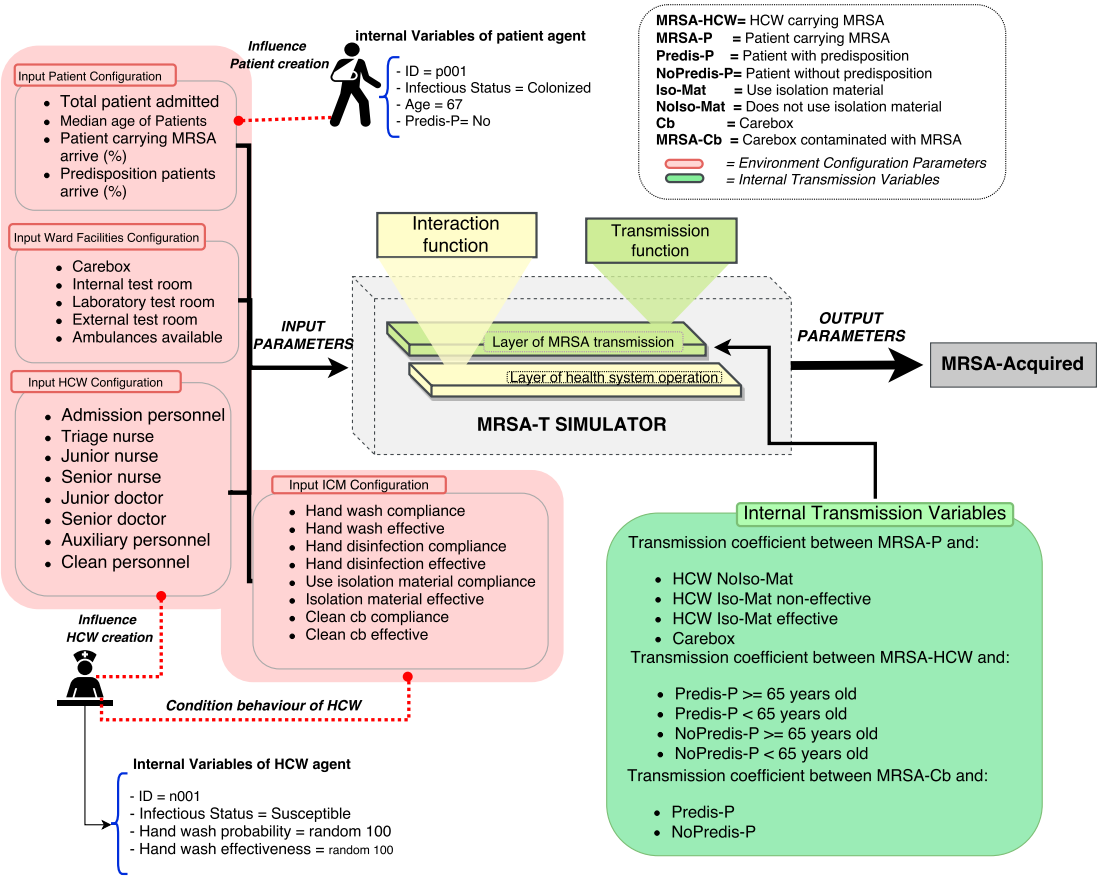


Figure 3: MRSA-T-Simulator: Environment Configuration Parameters and Internal Transmission Variables

3 Design the Virtual Clinical Trial

The process followed to obtain our VCTs is based on the fact that we have a tool to simulate MRSA contact transmission, and this tool is highly configurable. Therefore, we are able to calibrated the simulator through give values to **Environment Configuration Parameters** and **Internal Transmission Variables**, such as described in Section 2.2. If our simulation tool is able to reproduce the results shown in the real CT, we can conclude that the tool is properly configured for the studied environment. Based on this configuration, we can make some modifications, only on the **Environment Configuration Parameters** with the aim to create other scenarios, simulate these, and obtain predictions. It is worth noting that **Internal Transmission Variables** only change during the calibration process of the tool.

3.1 Source of Data: Clinical Trial in Hospital Ward

When working in simulated environments, it is very important to have input data from reliable sources. In our case, considering that the purpose of this research is to adjust the simulation tool developed to obtain VCTs, we have taken as a main data source the work of Roisin et al.

[17], which details step by step the design and execution of a cross-over trial to determine the efficacy of a rapid MRSA screening test, which is called a PCR (Polymerase-chain reaction) test compared to the culture test at the time of patients' hospital admission. Therefore, the total number of patients who participate in the study is divided into **Intervention Case** (PCR test) and **Control Case** (Culture test). The data, which cannot be extracted from this research, has been taken from other investigations. Table 1 summarizes a list of variables with their respective values, which has been taken from Roisin et al [17]. These values are used to generate the Environment Configuration Parameters for our simulation. The percentage of MRSA acquisition obtained at the end of the study is also showed (MRSA-Acq). This MRSA-Acq percentage will be the final value that we must obtain as the main data output of our simulation.

Table 1: Data obtained of Roisin et al. research.

Input Data		
Characteristics	**Intervention Case**	**Control Case**
	Value	**Value**
Study Period (months)	11.5	11.5
No. of admissions	3182	3251
No. elegible admissions (stay <48h)	1788	1916
No. evaluable patients	1233	1272
No. NO-evaluable patients	555	644
Median (range) age (years)	67(17-101)	69(15-99)
Median (range) lenght of stay (days)	8(3-182)	8(3-108)
No. of surgical admission	236	268
No. of medical admission	997	1004
Patients MRSA culture positive on admission	170	151
Patients at risk on admission	1063	1121
% Hand hygiene compliance (No. appropiate /No.observed hand hyg.opportunities)	73.9	63.4
% MRSA patient isolation compliance (No.correct precautions /No. patient observations)	79.8	76.6
Output Data		
Characteristics	**Intervention Case**	**Control Case**
	Value	**Value**
Patients MRSA Acquisition during hospital stay	34	36
% MRSA Acquisition during hospital stay (MRSA-Acq) (No. cases /No.patients at risk)	3.2	3.2

3.2 Configuration of MRSA-T-Simulator. Parameters and Values

With the data provided in [17], we defined a first set of experiments with the aim of carrying out the calibration process of our model. The specific values used for Environment Configuration Parameters are defined in Table 2. In the case of the specific values used for the input HCW configuration, we do not have data available about the number of doctors, nurses, auxiliary staff or cleaning staff working in this environment, but we can define these values taking into account the configurations used in similar heathcare environments [16], the attention time (approximately) for each patient and the flow of patients into wards. We use the same HCW configuration to simulate PCR and Culture Cases. The behavior of HCWs is determined by the values of Input ICM Configuration. The patient population is defined by the Input Patient Configuration. A parameter that is not describe in the study is the percentage of patients with predisposition to acquire MRSA who arrive to the ED. For this parameter, we decided to use the **No. of surgical admissions** (Table 1), because the surgical patients are especially susceptible to acquiring MRSA. And finally, the ward facilities configuration have been established in such a way that there is always a carebox available for a new patient and no queues are created.

The values fixed for the Internal Transmission Parameters are showed in Table 3. These values don't change thoughout all the experiments.

Table 2: Values to Environment Configuration Parameter

Description	Value
Admission Personnel	1
Triaje Nurse	2
Senior Clinical Nurse	5
Junior Clinical Nurse	7
Senior Doctor	5
Junior Doctor	5
Auxiliary Personnel	1
Cleaning Personnel	1

(a) Input HCW Configuration.

Description	Value
Number of Carebox	100
Number of Internal test room	3
Number of Laboratory test room	3
Number of External test room	3
Number of Ambulance	1

(b) Input Ward Facilities Configuration.

Description	Value	
	PCR	Culture
Total patients arrive	3182	3251
Median age of patients	67	67
Percentage of MRSA patients arrive	14%	12%
Percentage of patients with predisposition to arrive	20%	20%

(c) Input Patient Configuration.

Description	Value	
	PCR	Culture
Hand disinfection compliance	74%	63%
Hand disinfection effective*	80%	80%
Use of Isolation material compliance	80%	80%
Use of Isolation material effective*	80%	80%
Clean Carebox compliance*	80%	80%
Clean Carebox effective*	80%	80%

* Assumed based on the high level of compliance with ICM described.

(d) Input ICM Configuration.

Table 3: Values for Internal Transmission Variables

Description	Value
Transmission coefficient between MRSA-P and...	
Patient with predisposition >= 65 years old	0.05
Patient with predisposition <65 years old	0.03
Patient without predisposition >= 65 years old	0.02
Patient without predisposition <65 years old	0.02
Transmission coefficient between MRSA-P and...	
HCW which does not use isolation material	0.05
HCW which uses isolation material but isolation is not effective.	0.02
HCW which uses isolation material and the isolation is effective.	0.00
Carebox	1.00
Transmission coefficient between MRSA-Cb.	
Patient with predisposition	0.03
Patient without predisposition	0.01

4 Virtual Clinical Trials Results

All experiments were executed in parallel on 2-node cluster with 64 cores per compute node: CPU AMD Opteron6262 HE. For each configuration 192 repetitions were carried out. The right number of repetitions is defined based on statistical methods applying for a non-terminated system[3] to achieve statistically meaningful results. We compute the average of total number of repetitions for each scenario. A warm-up period of 2000 hours was defined to get the state ready of the system. The simulation time was 8280 hours, corresponding to 11.5 months of real CT duration. Principal outcome data for each repetition is the MRSA-Acq(%).

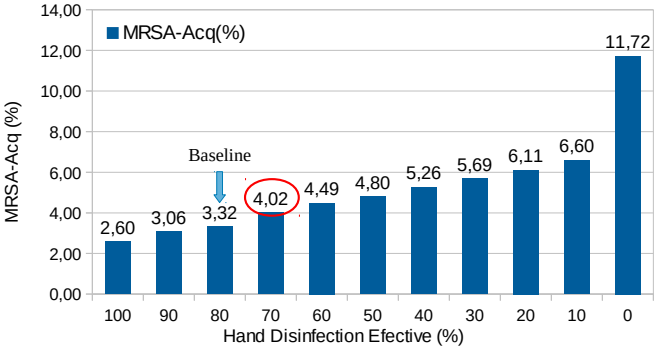
Table 4: Compared between simulation and real values.

Definition	Intervention Case Value (PCR)		Control Case Value (Culture)	
	Real	Simulation	Real	Simulation
Total patients admitted	3182.00	3182.00	3251.00	3251.00
Patients not included (=<48H, death, etc)	1949.00	1936.31	1979.00	1981.47
Patients included (>48h)	1233.00	1245.69	1272.00	1269.53
Patients susceptible at admission	1063.00	1071.25	1121.00	1195.09
Patients carrying MRSA at admission	170.00	174.44	151.00	174.44
Patients included who acquired MRSA (MRSA-Acq)	34.00	33.89	36.00	37.02
Patients included who acquired MRSA(MRSA-Acq %)	3.20	3.16	3.21	3.32

* Assumed on base of MRSA imported value of paper.

Stage 1: Reproducing a CT

Our model reproduces a stochastic process, where results depend on several factors such as the initial parameters and the behavior of the agents. Therefore, setting a relative error value is necessary. This error determines a range of values for which the results will be valid. In this case, we fixed the error permitted as **MRSA-Acq** $\pm$ σ. Where MRSA-Acq = 3.2% (percentage calculated respect to patients susceptible), and σ $\pm$10%. Thus, the range of values is [2.88-3.52]% for Intervention Case and [2.89-3.53]% for Control Case. Output data of VCTs are shown in Table 4. As can be seen, the results for MRSA-Acq, both for Intervention and Control Case, are within the correspondent error range. Therefore, we conclude that the MRSA-T-Simulator is calibrated for the studied environment and it is able to design and execute VCTs with valid results. These two simulated scenarios are the baseline to create new study scenarios.



(a)

VCT	HW-Effect	Patients included VCT (>48h)	Patients MRSA-Acq	Patients MRSA-Acq(%)
1	100	1277,23	29,23	2,60
2	90	1274,27	34,38	3,06
3	80	1269,53	37,02	3,32
4	70	1277,50	45,27	4,02
5	60	1274,64	50,28	4,49
6	50	1269,91	53,55	4,80
7	40	1276,09	59,04	5,26
8	30	1272,83	63,67	5,69
9	20	1275,91	68,48	6,11
10	10	1271,87	73,86	6,60
11	0	1275,27	131,31	11,72

Baseline

(b)

Figure 4: (a) Percentages of MRSA-Acq(%) for 11 VCTs. (b) Output data for 11 VCTs based on Control Case. A decrement of Hand Wash Effective variable is apply in each VCT.

Stage 2: Using MRSA-T-Simulator as predictive tool

The simulator allow us acquire new knowledge or respond a specific clinical problem through the design and execution new VCTs. Such as a real CT, the VCT needs to answer a specific question. Thus, we consider the following hypothetical case where HCWs demand to know what is the minimum effective disinfection value of hands to generate an MRSA-Acq <4.5%. We assumed for this VCT the same configuration of the Control Case. To answer this question,

we propose the execution of several VCTs in which the variable Hand Disinfection Effective takes different values that allow us to determine what would be the sought value. It is important to remark that, except this variable, the initial configuration of the simulation should not be modified (Fig. 4). The range of values for Hand Disinfection Effective is [100 - 0]%. We know that extreme cases, 100% and 0%, are not possible in a real environment; however these are considered as part of the example to highlight differences between the two extreme cases. It can be deduced that, as long as the percentage of effective disinfection of the hands remains within the range [100, 70]%, MRSA-Acq will be less than 4.5%. However, when the hand disinfection effective percentage drops below 70%, the percentage of patients who acquire MRSA reaches the threshold. In a real environment, analysis of this type are not possible due to the ethical implications that, non-compliance (premeditated) of ICMs by HCWs would entail.

5 Conclusions and Future Work

- We developed a model and a simulator of MRSA contact transmission, highly configurable, using the ABMS approach. The simulator is a flexible tool that allow several configurations to the patients population, HCWs, and the ward facilities. This configuration is achieved by giving specific values to the simulator variables.
- MRSA-T-Simulator allows us to replicate a real CT, in order to analyce and predict the probably consequences that some changes in the design of the original CT could entail. The results are obtained in a period of time less than a real CT. It allow us to avoid the need to design and carry out a new CT.
- Our simulation tool helps us to design, execute and obtain results of VCTs which in real life are not possible for ethical, economic or time reasons.
- As a future work, we plan to include the transmission of MRSA among HCWs to HCWs. In addition, due to MRSA can be transmitted through physical contact, other passive agents, such as electronic devices, could be introduced into the simulation model.

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References

[1] Björn Bornkamp, Frank Bretz, Alex Dmitrienko, Greg Enas, Brenda Gaydos, Chyi-Hung Hsu, Franz König, Michael Krams, Qing Liu, Beat Neuenschwander, et al. Innovative approaches for designing and analyzing adaptive dose-ranging trials. *Journal of biopharmaceutical statistics*, 17(6):965–995, 2007.

[2] Farida Chamchod and Shigui Ruan. Modeling the spread of methicillin-resistant staphylococcus aureus in nursing homes for elderly. *PLoS ONE*, 7(1):1–9, 01 2012.

[3] Christopher A Chung. *Simulation modeling handbook: a practical approach*. CRC press, 2003.

[4] Sara E Cosgrove, Youlin Qi, Keith S Kaye, Stephan Harbarth, Adolf W Karchmer, and Yehuda Carmeli. The impact of methicillin resistance in staphylococcus aureus bacteremia on patient outcomes: mortality, length of stay, and hospital charges. *Infection Control & Hospital Epidemiology*, 26(02):166–174, 2005.

[5] EJ Fendler, Y Ali, BS Hammond, MK Lyons, MB Kelley, and NA Vowell. The impact of alcohol hand sanitizer use on infection rates in an extended care facility. *American journal of infection control*, 30(4):226–233, 2002.

[6] Cecilia Jaramillo, Manel Taboada, Francisco Epelde, Dolores Rexachs, and Emilio Luque. Agent based model and simulation of mrsa transmission in emergency departments. *Procedia Computer Science*, 51:443–452, 2015.

[7] RL Lalonde, KG Kowalski, MM Hutmacher, W Ewy, DJ Nichols, PA Milligan, BW Corrigan, PA Lockwood, SA Marshall, LJ Benincosa, et al. Model-based drug development. *Clinical Pharmacology & Therapeutics*, 82(1):21–32, 2007.

[8] Zhengchun Liu, Eduardo Cabrera, Manel Taboada, Francisco Epelde, Dolores Rexachs, and Emilio Luque. Quantitative evaluation of decision effects in the management of emergency department problems. *Procedia Computer Science*, 51:433–442, 2015.

[9] Peter A Lockwood, Jack A Cook, Wayne E Ewy, and Jaap W Mandema. The use of clinical trial simulation to support dose selection: application to development of a new treatment for chronic neuropathic pain. *Pharmaceutical research*, 20(11):1752–1759, 2003.

[10] Charles M Macal and Michael J North. Tutorial on agent-based modeling and simulation. In *Proceedings of the 37th conference on Winter simulation*, pages 2–15. Winter Simulation Conference, 2005.

[11] Yang Meng, Ruth Davies, Katherine Hardy, and Peter Hawkey. An application of agent-based simulation to the management of hospital-acquired infection. *Journal of Simulation*, 4(1):60–67, 2010.

[12] L Milazzo, James L Bown, A Eberst, G Phillips, and JW Crawford. Modelling of healthcare associated infections: a study on the dynamics of pathogen transmission by using an individual-based approach. *Computer methods and programs in biomedicine*, 104(2):260–265, 2011.

[13] World Health Organization. International standards for clinical trial registries. [online], 2012. `http://apps.who.int/iris/bitstream/10665/76705/1/9789241504294_eng.pdf?ua=1`.

[14] John Orloff, Frank Douglas, Jose Pinheiro, Susan Levinson, Michael Branson, Pravin Chaturvedi, Ene Ette, Paul Gallo, Gigi Hirsch, Cyrus Mehta, et al. The future of drug development: advancing clinical trial design. *Nature Reviews Drug Discovery*, 8(12):949–957, 2009.

[15] Didier Pittet. Compliance with hand disinfection and its impact on hospital-acquired infections. *Journal of Hospital Infection*, 48:S40–S46, 2001.

[16] Janet Raboud, Refik Saskin, Andrew Simor, Mark Loeb, Karen Green, Don E Low, and Allison McGeer. Modeling transmission of methicillin-resistant staphylococcus aureus among patients admitted to a hospital. *Infection Control & Hospital Epidemiology*, 26(07):607–615, 2005.

[17] Sandrine Roisin, Christine Laurent, Olivier Denis, Michèle Dramaix, Claire Nonhoff, Marie Hallin, Baudouin Byl, and Marc J Struelens. Impact of rapid molecular screening at hospital admission on nosocomial transmission of methicillin-resistant staphylococcus aureus: cluster randomised trial. *PloS one*, 9(5):e96310, 2014.

[18] Véronique Sébille and Alain-Jacques Valleron. A computer simulation model for the spread of nosocomial infections caused by multidrug-resistant pathogens. *Computers and biomedical research*, 30(4):307–322, 1997.

[19] LB Sheiner and J-L Steimer. Pharmacokinetic/pharmacodynamic modeling in drug development. *Annual review of pharmacology and toxicology*, 40(1):67–95, 2000.

[20] European Union. Council recommendation of 9 june 2009 on patient safety, including the prevention and control of healthcare associated infections. `http://eur-lex.europa.eu/legal-content/en/ALL/?uri=OJ:C:2009:151:TOC`, last viewed January 2016, 2009.

[21] P Zarb, B Coignard, J Griskeviciene, A Muller, V Vankerckhoven, K Weist, M Goossens, S Vaerenberg, S Hopkins, B Catry, et al. The european centre for disease prevention and control (ecdc) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. *Euro Surveill*, 17(46):20316, 2012.