Appendix A

ODD protocol (*Overview, Design concepts, Details*)

OVERVIEW

1. Purpose

Using an agent-based model (ABM) approach, the present study aimed to simulate the transmission of vancomycin-resistant enterococci (VRE) within and between three hospital care units, according to different infection prevention and control (IPC) measures, namely standard precautions (SP), additional contact precautions (CP), geographical cohorting of carrier patients and creation of an isolation unit with dedicated staff.

The ABM was constructed on the framework of short-stay medical wards, represented by 2 conventional units (CU) and 1 intensive care unit (ICU), with single rooms. In one of the scenarios, an isolation unit devoted to patients with VRE (CU with a dedicated healthcare team) was added.

1. Entities, state variables and scales

This model consisted of a discrete event system. Each time step is called *tick*.

The time scale: one *tick* represented a period of 15 minutes. The simulations were carried out over a period of 1 year. We run 50 simulations.

**The different entities of the model are**:

* Individuals with different types:
	+ **Patients**, characterized by:
		- Length of stay (on each admission to a unit)
		- Inpatient or outpatient
		- Cumulative number of hospitalizations
		- Having had a link and a care with a caregiver (for each caregiver)
		- Be on or off antibiotics (VRE-selective antibiotics)
		- VRE-carrier or not
		- Contagious (patients shedding VRE) or not
		- Contagiousness duration (see duration of shedding VRE in the table below)
		- Delay of detection (delay between the contamination and the result of microbiological analysis)
		- Count of carrying time (since contamination)
		- Known VRE-carriage (when result of microbiological analysis is known)
		- Known carrier patients shedding VRE (eligible patients for CP, cohorting or isolation unit)
	+ **Registered nurses (RN), nursing assistants (RNA), medical interns and senior physicians,** characterized by:
		- Working time
		- Contaminated hands or not
* Links between different persons: undirected links from caregivers to patients (resulting in RN-links, RNA-links, interns-links and physician-links)
* Spatial units, made up of:
	+ 2 conventional units (CU 1 and CU 2) on grid of 6 x 12 cells (patches)
	+ 1 intensive care unit (ICU) on grid of 4 x 12 patches
	+ In one scenario: 1 isolation unit on grid of 6 x 12 patches

One room corresponds to one patch.

* + The other patches of area correspond to outside of our short-stay medical ward (other ward, home, etc.)
* Environment:
	+ Patient behavior: admission and discharge of unit, either to another unit or to outside
	+ Caregiver behavior: patient care (contact with a patient). Movements of different categories of caregiver depend to time of day and time of week.
* Temporal scale: we have created time variables (minutes, hours and days) to differentiate period of work: morning, evening, night, day, Saturday, Sunday, doctor night/weekend shift
1. Process overview and scheduling

The model was constructed with the NetLogo software version 6.1.1.

On every tick, the **chronologic** **process** is:

1. Update of ticks
2. Update of variables of time (minutes, hours, days)
3. Update of indication of time (morning, evening, etc.)
4. Update of contagiousness duration and count of carrying time for VRE-carrier patients
5. Update of patient status for VRE-carrier patients whose carrying duration reaches the delay of detection (becomes know VRE-carriers)
6. Evaluation of contagiousness patient status [see submodel *non-excreteur* in attached program]
7. Evaluation of patient eligibility for ICP measures [see *a-regrouper*]
8. Evaluation of isolation unit establishment [see *activation-cohorting*]
9. Evaluation of isolation unit closing [see *arret-cohorting*]
10. Evaluation of cohorting implementation [see *activation-regroupement*]
11. Evaluation of cohorting lifting [see *arret-regroupement*]
12. If isolation unit, setting up an isolation unit [see *create-cohorting*]
13. If isolation unit, evaluation of the number of caregivers in the dedicated unit [see *effectif-cohorting*]
14. Evaluation of patient discharge [see *sortie-patients*]
15. Evaluation of patient admission [see *entree-patients*]
16. If isolation unit, transfer of eligible patients to the isolation unit [see *transfer-cohorting*]
17. If cohorting, transfer of eligible patients to the cohorting [see *transfer-regroupement*]
18. Evaluation of the need to provide care for each caregiver [see *soins-XXX*]
19. Update of working time for each caregiver [see *update-XXX*]
20. Evaluation of shift in care
21. Update length of stay for inpatient
22. Creation of VRE-case when time reaches 6 months
23. Stopping the model if the time is equal to 1 year

CONSTRUCTION

1. Design concepts

***Basic principles, interaction, adaptation, prediction et stochasticity***

The model was developed to simulate the patient-to-patient **transmission** of VRE, solely by the hands of personnel who become contaminated during contact with a contagious VRE-carrier (patient shedding VRE).

Hypotheses are:

* No direct patient-to-patient or caregiver-to-caregiver transmission
* No contamination of environment (surfaces or equipment)
* The probability of transmission of VREs from the caregiver to the patient and that of the patient to the caregiver are different. There is no different type of care, but these probabilities are not fixed (beta distribution, see table below).
* VRE-selective antibiotics are a risk factor associated with VRE-colonisation (OR=3.5)
* Hand hygiene (HH) before and after a care intervention is performed with a compliance fixed for all caregivers (compliance differs according to the scenarios).
* Number of caregivers per unit depends on to time of day, unit and type of caregiver. This number is taken from observed data (see table below).
* When a caregiver starts day of work, their hands are not contaminated.
* The number of care (contact with patient) is defined according to type of caregiver, time of day, time of week and caregiver-patient ratio.
* No sharing caregivers between units except the intern night shift and on Saturday mornings for senior physicians (except isolation unit).

At each simulated care, the probability of VRE-transmission was calculated 1) on the basis of the probability of transmission from the patient to the caregiver, for a care at a contagious patient. The caregiver hands remained contaminated if he had not been hand hygiene compliant after the care. The chance of a caregiver being compliant depended on the scenario (% HH) and the patient (VRE-carrier or not). 2) on the basis of the probability of transmission from the caregiver to the patient, for a care done by contagious caregiver (i.e. with contaminated hands). The caregiver was contagious if he had not been hand hygiene compliant before the care. If the patient was receiving antibiotics, the transmission probability was increased (multiplied by antibiotics odd ratio). These parameters were defined in the table below.

**Patient movement** is taken into account: admission and discharge, and transfer between units.

Hypotheses are:

* No transfer from isolation unit to other unit
* Units are not always full
* Mean length of stay is taken from observed data for each unit. They are defined randomly at each admission (lognormal distribution, see table below)
* A patient can have several hospitalizations
* Patients who have already been hospitalized are less likely to be drawn to be hospitalized again
* The unit of admission is randomly according to probability of admission in each unit (observed data)
* They are no deaths during the one-year simulation

Patient can have different **status of VRE-carriage**:

* No VRE-carriage (no positive sample)
* Not known carrier patients shedding VRE (it has just been contaminated, he is contagious, but he has not yet been detected)
* Known carrier patients shedding VRE (he is contagious and has been detected)
* Known VRE-carriage but not shedding (he is no longer contagious because the time to clearance has passed, see duration of shedding VRE in the table below)

Hypotheses are:

* Patient is detected because of screenings (active surveillance). A day is defined for the screenings (weekly screening at Tuesday (day 2)). The microbiological analysis result is known after 96 hours. After that, patient is detected (known VRE-carriage patient).
* The shedding duration is defined randomly when patient is contaminated, according observed data (gamma distribution, see table below). When shedding period is finished, patient still be VRE-carriage but no longer shedding (no longer contagious).
* Patient can be contaminated several times (go back VRE-shedding patient, but he is not considered a new case)
* VRE-carrier patient remains VRE-carrier until the end of simulation

**IPC measures** can be implemented in addition to SP (SP represented by HH):

* CP: are simulated by an increase of HH compliance rate for the care at known carrier patients shedding VRE.
* Cohorting: for known carrier patients shedding VRE (eligible patient) in CU 1.
* Isolation unit: for known carrier patients shedding VRE (eligible patient), with dedicated caregivers.

Hypotheses are:

* Transfer of eligible patients from ICU to isolation unit is not forced (they go out according to length of stay)
* Threshold of implementation and lifting of cohorting and isolation unit are fixed according to scenario

***Observation and emergence***

In order to evaluate the impact of IPC measures, number of new VRE-cases is counted at each step. The primary endpoint was the cumulative number of VRE-cases at the end of the simulations.

***Detection***

In order to differentiate different units and outside, global variables are created, as well as global variables for the rooms in each unit. In order to identify which caregiver provides care to which patient, undirected links are created and deleted for each care.

DETAILS

1. Initialization

At time t = 0, initial conditions are:

* The simulation starts at 6:00 AM of day 1, week 1, month 1
* Aera is created: 2 CU, 1 ICU, outside +/- isolation unit
* Caregivers are created
* Patients are created: 1,250 patients (according to the observed number of patients hospitalized in the 3 reference units over one year) distributed as follows:
	+ Inpatients:
		- 17 patients in CU 1
		- 19 patients in CU 2
		- 7 patients in ICU
		- Count of hospitalization for each patient = 1
		- One of inpatients is chosen randomly to be contagious VRE-carriage, but not yet known. Screenings carry out next day (day 2 = Tuesday). The result is known after 96 hours. The minimum length of stay of this patient after detection is 2 days.
	+ Outpatients:
		- 4 outpatients are chosen randomly to be contagious VRE-carriage. They will be contagious at minimum 2 days.
		- The remaining 1,206 outpatients have a hospitalization count equal to 0 and are not VRE-carriers and are not on antibiotics.
* Cohorting and isolation unit are not implemented

Initial conditions are described in the table below.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Value** | **Range** | **Distribution** | **Reference** |  |
| ***Patients*** |  |  |  |  |  |
| Total number of patients | 1,250 | -  | -  | Observed data |  |
| Duration of shedding VRE (mean in month) | 6.7 | 10.9 (SD) | Gamma (a=0.61b=0.09) | Reference2 |  |
| Antibiotics OR (during detection hosp.) | 3.5 | - | -  | Reference3–6 |  |
| ***Caregivers*** |  |  |  |  |  |
| Working time of RN and RNA (hours) | 8 | -  | -  | Observed data |  |
| Working time of physicians (hours) |  |  |  |  |  |
| weekday | 10 | -  | -  | Observed data |  |
| Saturday morning | 3 | -  | -  | Observed data |  |
| night shift | 14 | -  | -  | Observed data |  |
| Saturday shift | 21 | -  | -  | Observed data |  |
| Sunday shift | 23.5 | -  | -  | Observed data |  |
| ***CU 1 and 2*** |  |  |  |  |  |
| Number of beds in CU 1 | 17 | -  | -  | Observed data |  |
| Number of beds in CU 2 | 19 | -  | -  | Observed data |  |
| Proportion of admissions to CU 1 | 0.35 | - | - | Observed data |  |
| Proportion of admissions to CU 2 | 0.43 | - | - | Observed data |  |
| Proportion of admissions to CU 1 | 0.18 | - | - | Observed data |  |
| Proportion of patients on antibiotics in CU 2 | 0.16 | - | - | Observed data |  |
| Length of stay CU 1 (mean in day) | 6.7 | 8.1 (SD) | Log normal | Observed data |  |
| Length of stay CU 2 (mean in day) | 5.7 | 7.1 (SD) | Log normal | Observed data |  |
| Probability of transfer from CU 1 to CU 2 | 0.017 | - | - | Observed data |  |
| Probability of transfer from CU 1 to CU SI | 0.063 | - | - | Observed data |  |
| Probability of transfer from CU 2 to CU 1 | 0.013 | - | - | Observed data |  |
| Probability of transfer from CU 2 to CU SI | 0.140 | - | - | Observed data |  |
| Number of RN morning and afternoon | 2 | -  | -  | Observed data |  |
| Number of RN night | 1 | -  | -  | Observed data |  |
| Number of RNA morning | 2 | -  | -  | Observed data |  |
| Number of RNA afternoon, night, weekend | 1 | -  | -  | Observed data |  |
| Number of senior physicians weekday | 1 à 2 | -  | -  | Observed data |  |
| Number of medical interns weekday | 1 |  |  | Observed data |  |
| ***ICU*** |
| Number of beds | 7 | -  | -  | Observed data |  |
| Proportion of admissions to ICU | 0.22 | - | - | Observed data |  |
| Proportion of admissions to ICU | 0.25 | - | - | Observed data |  |
| Length of stay (mean in day) | 3.4 | 4.2 (SD) | Log normal | Observed data |  |
| Probability of transfer from ICU to CU 1 | 0.339 | - | - | Observed data |  |
| Probability of transfer from ICU to CU 2 | 0.322 | - | - | Observed data |  |
| Number of RN morning, afternoon | 3 | -  | -  | Observed data |  |
| Number of RN night | 2 | -  | -  | Observed data |  |
| Number of RNA morning, weekday afternoon | 1 | -  | -  | Observed data |  |
| Number of RNA weekend afternoon, night | 0 | -  | -  | Observed data |  |
| Number of senior physicians weekday | 2 | -  | -  | Observed data |  |
| Number of medical interns weekday | 1 |  |  |  |  |
| Number of interns night/wk shift (3 units) | 1 | -  | -  | Observed data |  |
| ***Isolation unit*** |
| Number of beds | 14 | - | - | Observed data |  |
| Length of stay (mean in day) | 15.2 | 17.8 (SD) | Log normal | Observed data |  |
| Number of RN morning, afternoon | 2 | -  | -  | Observed data |  |
| Number of RN night | 1 | -  | -  | Observed data |  |
| Number of RNA morning, afternoon, night | 1 | -  | -  | Observed data |  |
| Number of RN or RNA day | 1 | -  | -  | Observed data |  |
| Number of senior physicians weekday | 1 | -  | -  | Observed data |  |
| Number of medical interns weekday | 2 | -  | -  | Observed data |  |
| Number of interns night/wk shift (3 units) | 1 | -  | -  | Observed data |  |
| ***Transmissions of VRE*** |  |  |  |  |  |
| Probability of transmission from the patient to the caregiver | 0.40 | 0.13 (SD) | Beta (α = 5 β = 7.5) | Reference7–10 |  |
| Probability of transmission from caregiver to the patient | 0.11 | 0.03 (SD) | Beta (α = 11β = 89) | Reference9–11 |  |
| VRE: vancomycin-resistant enterococci; SD: standard deviation; OR : *odds ratio*; Antibiotics: VRE-selective antibiotics; RN: Registered nurses ; RNA: nursing assistants; CU: conventional unit; ICU: intensive care unit  |

1. Input data

Our model use input data that represent a process that varies over time: duration of shedding VRE, length of stay for each unit, probability of transmission. Variables distributions are shown in the table above.

Values are randomly calculated at each contamination (duration of shedding VRE), at each admission (length of stay) and at each contaminating care (probability of transmission).

1. Submodels

**Time** [see *update-date* in attached program]

Each tick represented a period of 15 minutes.

* At every tick, 15 minutes are added to the minutes variable. When the minutes variable has reached 60, it returns to 0 and 1 hour is added to the hours variable.
* When hours variable has reached 24, it returns to 0 and 1 day is added to days variable and weekdays variable.
* When weekdays variable has reached 8, it returns to 1.
* When days variable has reached 32, it returns à 1 and 1 month is added to months variable. The model takes into account the months with 30 days and 31 days.
* When months variable s reached 13, it returns to 1 and 1 year is added to year variables (and the model stops at 1 year)

**indication of the time of day and week** [see *indication-temps* in attached program]

We use Boolean variables to let the model know at what time of day and week it is: weekday (days 1 to 5), Saturday (day 6), Sunday (day 7), morning (hours 6 to 14), afternoon (hours 14 to 22), night (hours 22 to 6), night shift (hours 18:30 to 8:45), weekend shift (Saturday 12:00 to Monday 8:45).

**Care** [see *soins-XXX* in attached program]

* At the beginning of each working day (except senior physician in CU and night shift), each patient receives a care, one after the other (at every tick), from each category of caregiver, according to caregiver-patient ratio and value of link and care variables. When all patients have received care, at each tick, each caregiver can care patients randomly with a 10% probability.
* Senior physicians have contact with patients twice a week.
* Medical interns have contact with all the patients of ICU at Sunday morning. At every tick during night shift, they have contact with patients of the 3 units randomly with a 10% probability. For isolation unit, this probability is equal to 3%.

**Shift of caregivers** [see *update-XXX* and *setup-XXX* in attached program]

Working times of each category of caregivers are indicated in the table above. When working time is reached, caregivers disappear, and links and care variables are updated. New caregivers are created.

**Admission and discharge of patients** [see *sortie-patients* and *entrée-partients* in attached program]

* Admission, discharge of hospitalization and the destination of discharge are evaluated at each tick according to parameters of table above.
* Discharged patients may be readmitted to hospital over the year. The number of rehospitalizations per patient has been calibrated to observed data.

**VRE-carriage** [see *soins-XXX* in attached program]

Contamination can occur during care: contamination of caregiver hands or contamination of patients if one of them is “contagious”. This contamination occurs according to probabilities of transmission and antibiotics risk factor (see table above).

Variables “carriage”, “contagious”, “duration of shedding”, “clearance”, “delay of detection” are updated.

VRE-carriage patients no longer shed (not contagious) when the duration of shedding reaches “clearance”. Patients then become non-contagious (but still carriage).

**IPC measures** [see *hyg-mains, activation-cohorting, arret-cohorting, transfert-cohorting…* in attached program]

* HH and CP: before and after each care, caregiver can perform HH. Rate of compliance is variable according to scenario. In CP scenario, this rate is increased for the care of eligible patients.
* Cohorting and isolation unit: patients are transferred to cohorting or isolation unit if they are eligible and according to threshold of implementation and lifting.

At 6 months, one inpatient become contagious VRE-carriage, but he is not yet detected. The two introduced cases were counted in the number of carrier cases at the end of the simulations

After 1 year, model stop.

References

1. *Wilensky, U. 1999. NetLogo. Http://Ccl.Northwestern.Edu/Netlogo/. Center for Connected Learning and Computer-Based Modeling, Northwestern University. Evanston, IL.*

2. Deboscker S, Lavigne T, Séverac F, Ménard C, Gaudart J, Meyer N. Épidémiologie des entérocoques résistants aux glycopeptides : 10 ans de suivi de patients porteurs dans un hôpital universitaire français. *Unpublished data*.

3. Deboscker S, Schneider P, Séverac F, et al. Factors associated with acquisition of glycopeptide-resistant enterococci during a single-strain outbreak. *Epidemiol Infect*. 2019;147(e158):1-8.

4. MacIntyre CR, Empson M, Boardman C, Sindhusake D, Lokan J, Brown GV. Risk factors for colonization with vancomycin-resistant enterococci in a Melbourne hospital. *Infect Control Hosp Epidemiol*. 2001;22(10):624-629.

5. McEvoy SP, Plant AJ, Pearman JW, Christiansen KJ. Risk factors for the acquisition of vancomycin-resistant enterococci during a single-strain outbreak at a major Australian teaching hospital. *J Hosp Infect*. 2006;62(2):256-258.

6. Karki S, Houston L, Land G, et al. Prevalence and risk factors for VRE colonisation in a tertiary hospital in Melbourne, Australia: a cross sectional study. *Antimicrob Resist Infect Control*. 2012;1:31.

7. Austin DJ, Bonten MJ, Weinstein RA, Slaughter S, Anderson RM. Vancomycin-resistant enterococci in intensive-care hospital settings: transmission dynamics, persistence, and the impact of infection control programs. *Proc Natl Acad Sci USA*. 1999;96(12):6908-6913.

8. D’Agata EMC, Horn MA, Webb GF. The impact of persistent gastrointestinal colonization on the transmission dynamics of vancomycin-resistant enterococci. *J Infect Dis*. 2002;185(6):766-773.

9. D’Agata EMC, Webb G, Horn M. A mathematical model quantifying the impact of antibiotic exposure and other interventions on the endemic prevalence of vancomycin-resistant enterococci. *J Infect Dis*. 2005;192(11):2004-2011.

10. Wolkewitz M, Dettenkofer M, Bertz H, Schumacher M, Huebner J. Environmental contamination as an important route for the transmission of the hospital pathogen VRE: modeling and prediction of classical interventions. *Infectious Diseases: Research and Treatment*. 2008;1:3-11.

11. Milazzo L, Bown JL, Eberst A, Phillips G, Crawford JW. Modelling of healthcare-associated infections: a study on the dynamics of pathogen transmission by using an individual-based approach. *Comput Methods Programs Biomed*. 2011;104(2):260-265.