Methicillin resistant *Staphylococcus aureus* transmission reduction using Agent-Based Modeling and Simulation

Sean Barnes
PhD Student, Applied Mathematics & Scientific Computation
University of Maryland, College Park
sbarnes@math.umd.edu

Dr. Bruce Golden
Professor, Robert H. Smith School of Business
University of Maryland, College Park
bgolden@rhsmith.umd.edu

Agenda

- Motivation
- Methodology
- Implementation
- Verification and Validation
- Additional Testing
- Conclusions
- Questions

Motivation

- The spread of infection is a huge problem, particularly in large, tertiary-care hospitals across the world
- One of the most prevalent types of infection is **Methicillin resistant *Staphylococcus aureus*** (MRSA), the cause of close to 300,000 hospital-acquired infections and 20,000 deaths per year in the US [Ref. 1]
- **Project Goals:**
  1. Model the transmission dynamics of MRSA within a hospital, primarily through simulating the direct interactions between health care workers and patients, and
  2. Test the effectiveness of various infection control measures on preventing the spread of MRSA

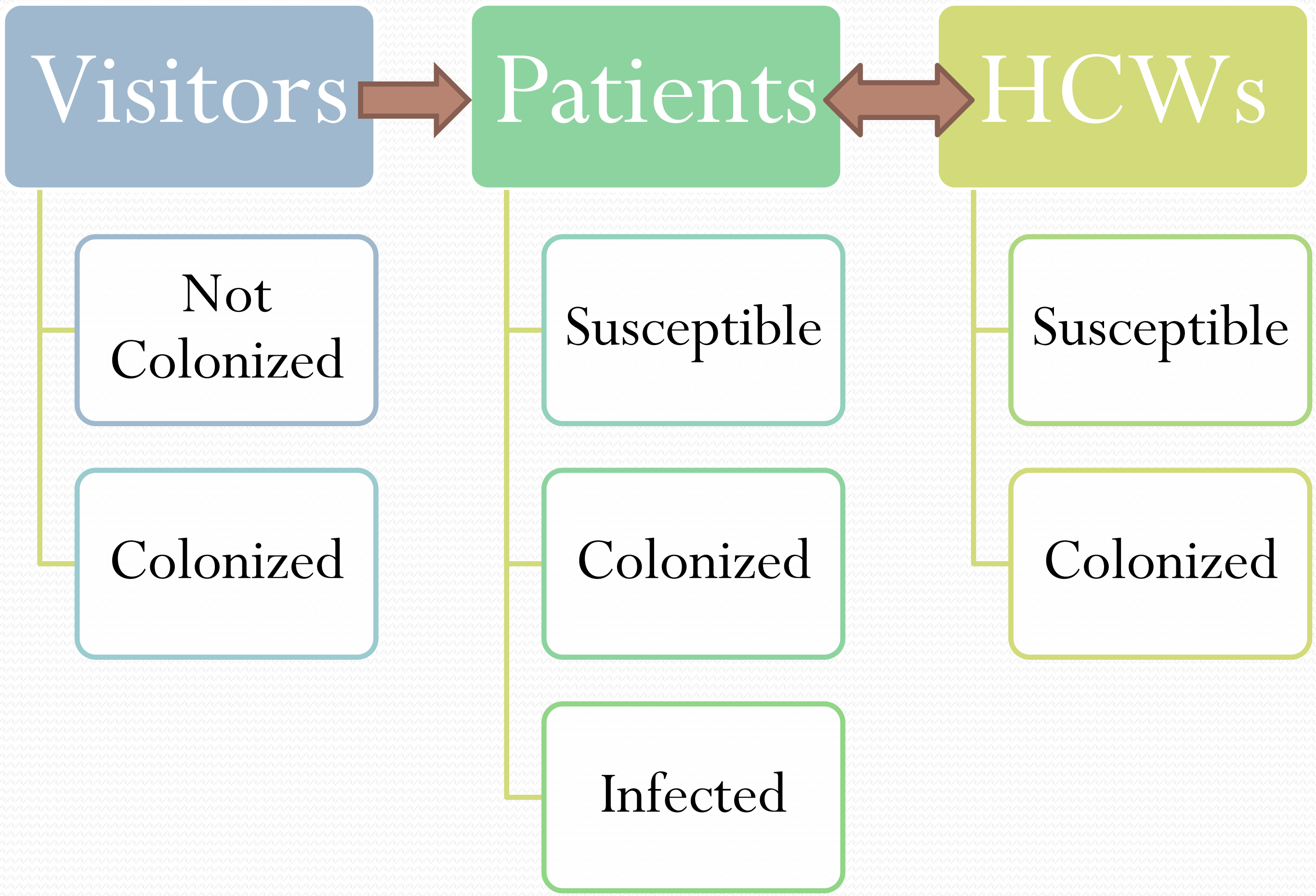
Methodology

- The majority of efforts on this problem have relied heavily upon equation based modeling [Refs. 2-7]
- The tractability of these methods depend on limiting assumptions that make it difficult to examine complex scenarios
- **Agent-based modeling and simulation (ABMS)** allows us to model explicitly the **interactions** between patients, health care workers, and visitors

ABMS

- Seeks to generate macroscopic (emergent) behavior from modeling microscopic interactions
- Easily allows for heterogeneity within the population
- Requires:
  - Definition of agents and their behaviors
  - Scope of interactions between agents
  - Optional: Explicit representation of the environment
- Agents:
  - Patients
  - Health care workers (HCWs, i.e. nurses and physicians)
  - Visitors
- The hospital serves as the environment where the agents interact

Agent States and Interactions



Implementation

- Stochastic agent-based simulation package developed in **Python** using various modules, most prevalently *SimPy* and *Parallel Python*
- SimPy: Discrete event simulation package which provides built-in functionality for simulating the interactions between agents and generating useful data
- Parallel Python: Multi-core parallel processing package which allowed for simultaneous execution of Monte Carlo simulation replications
- Agents were developed as object-oriented classes, with process execution methods defined for SimPy

Transmission Factors

- Hand hygiene compliance
- Hand hygiene efficacy
- HCW to patient ratios

Performance

- Transmissibility
  - Patient to HCW
  - HCW to Patient
  - Visitor to Patient
- Length of stay
- Number of daily contacts
- Proportion of colonized patients admitted

External

Infection Control Measures

- Patient screening
  - On admission (with some probability)
  - With some frequency during patient stay
- Patient isolation
  - Into single rooms
  - With some or no delay
- Decolonization
  - Colonized patients
  - Infected patients (Treatment)

Infection Metrics

- **Basic reproduction number, R_0**: Mean number of secondary cases as the result of a single primary case
- **Successful introduction rate**: No. of secondary cases
- **Attack rate**: Ratio of transmissions to uncolonized patient days
- **Colonized patient days**: Percentage of total days spent as a colonized or infected patient
- **Ward prevalence**: Percentage of days on which at least one colonized patient was present

User Interface

Input

- Parameter spreadsheet template
  - Simulation parameters
  - Hospital/staff definitions
  - Infection control policy
  - Additional paramaters
- Optional:
  - Parameter variations
  - Number of parallel processors

Output

- Print results to screen
  - Key parameters
  - Infection control policy
  - Simulation metrics
  - Run times
- Save results to file
- Plot results
- Event logging

Computing I

Small Case

- 100 days, 250 replications
- 10 single/10 double rooms
- 10 nurses/5 physicians
- 10 day length of stay
- 5 daily contacts
- No infection control measures

All testing was performed on Genome cluster machine: 32 processors/128 GB RAM

Results

N	Job Time Sum (s)	Run Times (s)	Speedup
1	747	747	-
2	752	377	1.98
4	746	188	3.97
8	752	96	7.78
16	761	50	14.94
32	941	33	22.64

Degradation in speedup due to extraction of results from larger number of processors

Computing II

Large Case

- 500 days, 25 replications
- 50 single/150 double rooms
- 50 nurses/20 physicians
- 10 day length of stay
- 5 daily contacts
- All infection control measures

All testing was performed on Genome cluster machine: 32 processors/128 GB RAM

Results

N	Job Time Sum (m)	Run Times (m)	Speedup
1	136.9	136.9	-
2	138.4	71.84	1.91
4	136.1	37.91	3.61
8	133.7	21.10	6.49
16	141.3	11.88	11.52
32	182.3	8.96	15.28

Degradation in speedup due to extraction of results from larger number of processors

Verification and Validation

- Verification -- Is the model implemented correctly?
  - Programmatic testing
  - Simple test cases and scenarios (i.e. corner cases, relative value testing)
  - Event logging
- Validation -- Does the model represent real world behavior?
  - Matching behavior from the literature
    - SIR Model – Kermack and McKendrick (1927) [Ref. 2]
    - Beggs, Shepherd, and Kerr (2008) [Ref. 7]
    - Other models [Refs. 3-6]

SIR Model

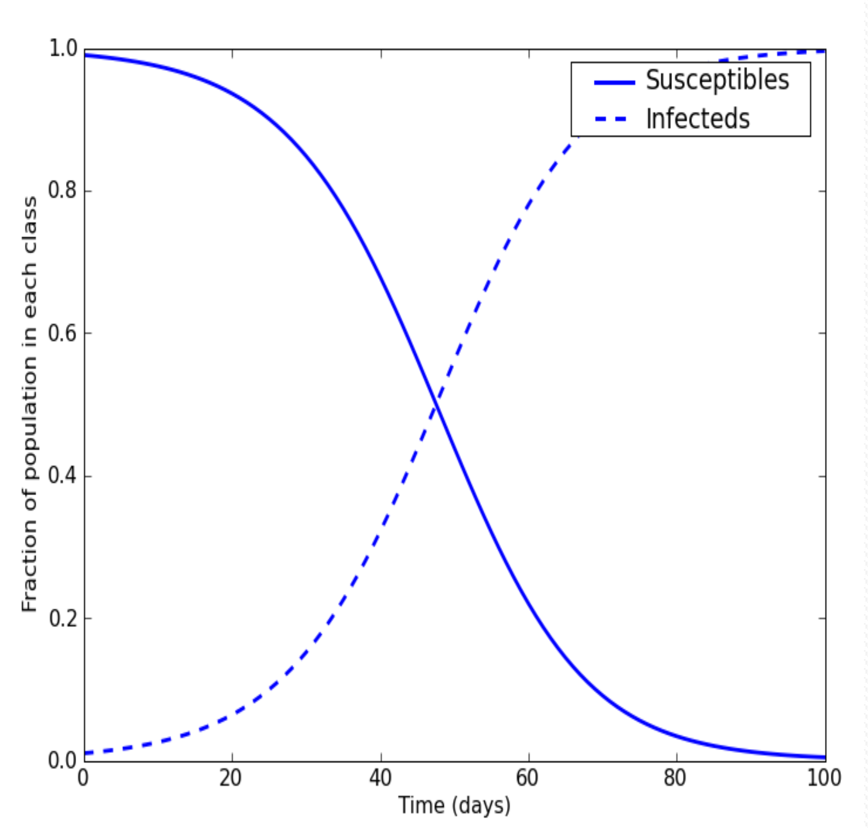
- Population transitions between **S**usceptible, **I**nfected, and **R**ecovered states
- Assumptions:
  - Closed population (i.e. no births, deaths, migration)
  - Homogeneous population, well-mixed
- Model equations:

$$\frac{dS}{dt} = -\beta SI, \ \frac{dI}{dt} = \beta SI - \gamma I, \ \frac{dR}{dt} = \gamma I$$

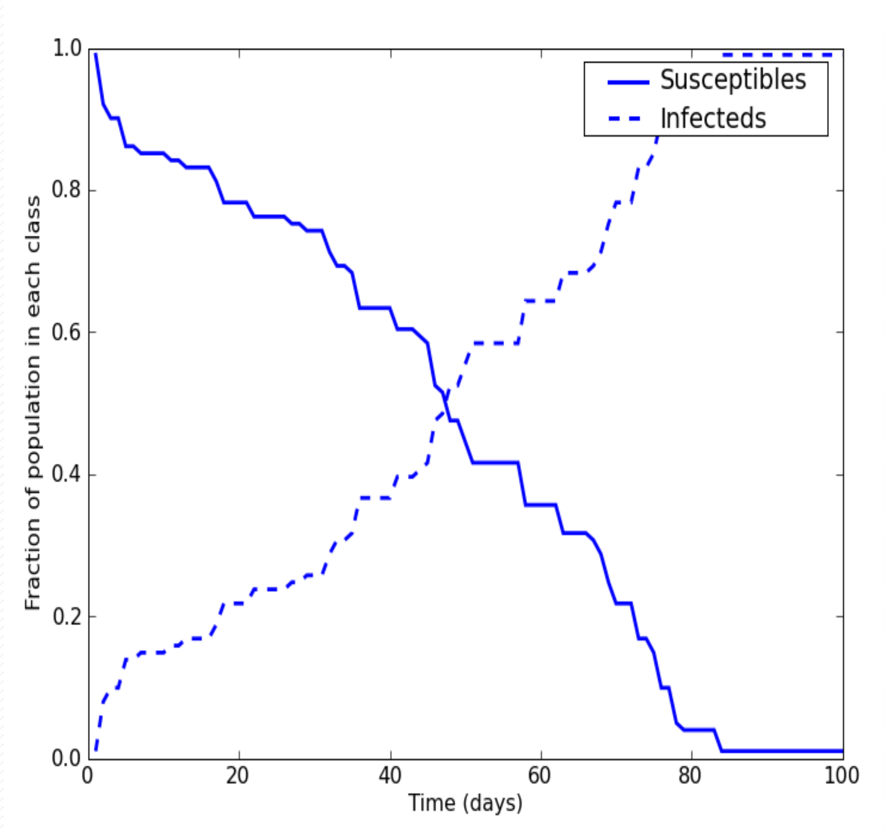
- Used to validate transmission dynamics of ABMS software

Comparison

SI Model



ABMS



Beggs, Shepherd, and Kerr Model

- Deterministic equation based model focused on demonstrating the limitations of hand hygiene compliance as a sole prevention measure
- Three coupled experiments:
  - Compliance vs. efficacy
  - Compliance vs. transmissibility
  - Compliance vs. daily contacts
- **Validation:** ABMS was able to reproduce trends in R_0 for all experiments, considering stochastic effects
- **Key Findings**
  - Compliance demonstrates diminishing returns
  - Transmissibility is the most dominating transmission factor

Targeting Zero

- Additional control measures are required to further reduce the incidence of transmission
- Baseline Case:
  - 100 days, 250 replications
  - 30 patients, 5 HCWs
  - 10 single, 10 double rooms
  - 5% of patients admitted are colonized with MRSA
  - 5 daily contacts per patient, U(0,10) day LOS
  - 50% hand hygiene compliance, 80% efficacy
  - No interventions

Comparison

Mean Statistic	Baseline	Isolation	Decolonization	Cohorting (1:1/2:1)	
Patients Colonized	51.46	39.56	45.42	**34.79**	40.65
Colonized Patients Admitted	36.50	34.48	34.76	**33.85**	33.89
No. of Secondary Cases	14.97	5.08	10.66	**0.94**	6.75
Ward Prevalence	82.51%	81.44%	**78.82%**	78.99%	80.57%
Colonized Patient Days	6.49%	5.66%	5.72%	**5.14%**	5.64%
Attack Rate	0.004989	0.001693	0.003553	**0.000313**	0.002251
R_0	0.4098	0.1474	0.3056	**0.0272**	0.1991

* Best case results shown for each infection control measure

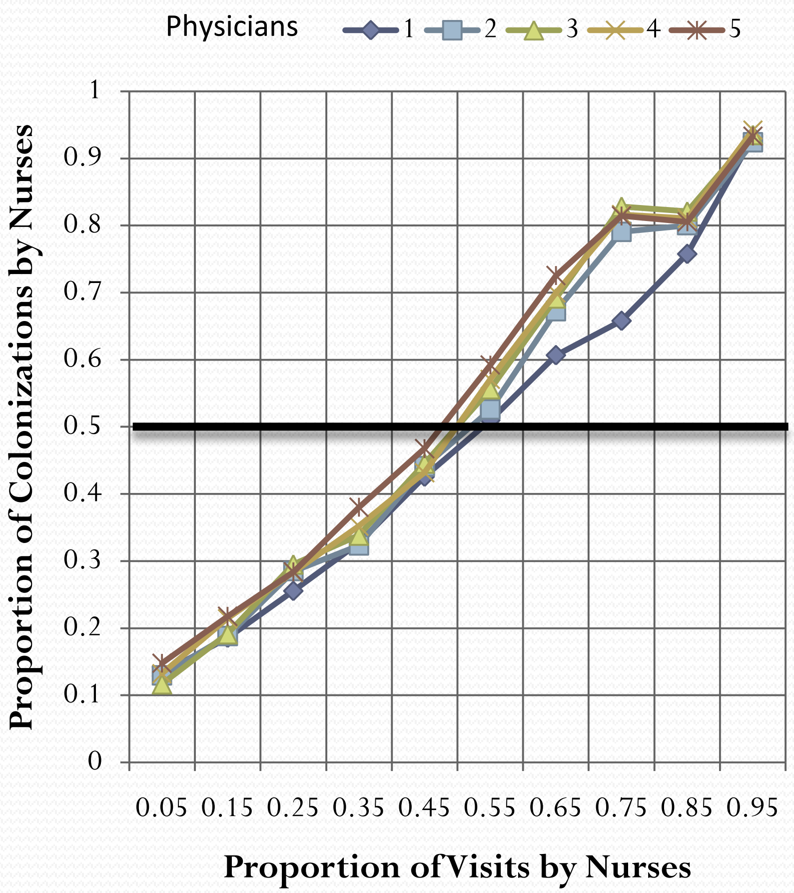
Additional Testing

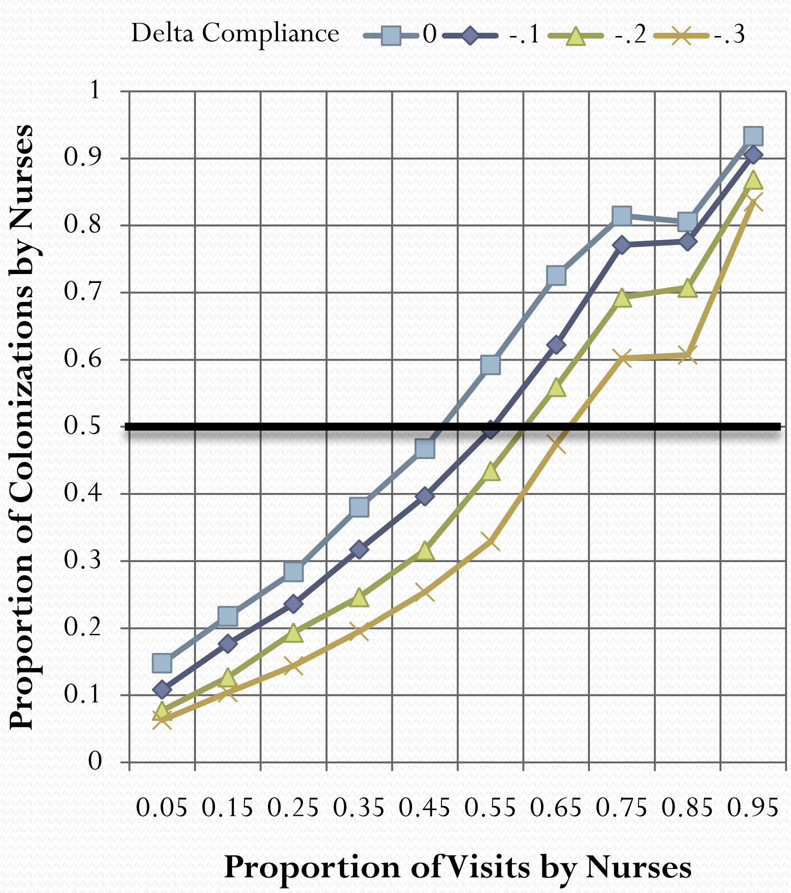
- A verified and validated AMBS software package allows us to perform a wide variety of *simulation experiments* to answer relevant questions

- Two Important Questions
  1. Do nurses or physicians spread more to patients?

  2. Could a 'good' hospital still be susceptible to an outbreak?

Who Spreads More?





Striving For Excellence

- Hospital: 100 patients, 20 nurses, 10 physicians
- 70% compliance, screening on admission, isolation, decolonization
- Hand hygiene efficacy, daily contacts, proportion of colonized admitted patients, screening test return times and patient lengths of stay do not have significant effects with high compliance
- But…the following cases can still lead to $R_0 > 1$:
  - Transmissibility > 0.28
  - Visitors > 200 per day (2% transmission rate) – Small world effect

Conclusions

- ABMS provides a powerful capability to explore complex systems
- Parallel processing provides a significant amount of speed up for running many replications for small cases, but large cases can still be prohibitively slow
- **Key Findings**:
  - Hand hygiene compliance is a crucial factor in transmission, but it demonstrates diminishing returns, necessitating additional measures
  - Nurses appear to spread more than physicians
  - Even the best hospitals are still susceptible to outbreaks
  - Best defense:
    1. Decreasing the connectivity of the patient network (isolation, low HCW-to-patient ratios) and
    2. Decreasing the likelihood of transmission by increasing compliance and efficacy and reducing transmissibility and daily contacts

Questions?

Acknowledgements

Dr. Radu Balan, University of Maryland

Dr. Aleksey Zimin, University of Maryland

Dr. Edward Wasil, American University

Dr. Anthony Harris, UMMC

Dr. Eli Perencevich, UMMC

Dr. Harold Standiford, UMMC

Dr. Carter Price, University of Maryland

Dr. Catherine Dibble, Aiki Labs

References

1. Committee to Reduce Infection Deaths. www.hospitalinfection.org
2. Kermack, WO and McKendrick AG, 1927. A Contribution to the Mathematical Theory of Epidemics. *Proc. Roy. Soc. Lond. A* , Vol. 115, pp. 700-721.
3. Austin DJ and Anderson RM, 1999. Studies of antibiotic resistance within the patient, hospitals and the community using mathematical models. *Phil. Trans. R. Soc. Lond. B*, Vol. 354, pp. 721-738.
4. Cooper BS, Medley GF, Scott GM, 1999. Preliminary analysis of the transmission dynamics of nosocomial infections: stochastic and management effects. Journal of Hospital Infection, Vol. 43, pp. 131-147.
5. Raboud J, Saskin R, Simor A, Loeb M, Green K, Low D, McGeer A, 2003. Modeling Transmission of Methicillin-Resistant *Staphylococcus Aureus* Among Patients Admitted To A Hospital. Infection Control and Hospital Epidemiology, Vol. 26 (7), pp. 607-614.
6. McBryde ES, Pettitt AN, McElwain DLS, 2007. A stochastic mathematical model of methicillin resistant *Staphylococcus aureus* transmission in an intensive care unit: Predicting the impact of interventions. Journal of Theoretical Biology, Vol. 245, pp. 470-481.
7. Beggs CB, Shepherd SJ, Kerr KG, 2008. Increasing the frequency of hand washing by healthcare workers does not lead to commensurate reductions in staphylococcal infection in a hospital ward. BMC Infectious Diseases, Vol. 8:114.