Registration form (basic details)

1a. Details of applicant

-Name, title(s): Martinus Christoffel Jozef (Martin) Bootsma, PhD
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-Doctorate (date, dd/mm/yyyy): 23/05/2005
-Use of extension clause: no

1b. Title of research proposal

Mathematical tools in support of infection prevention

1c. Summary of research proposal

(297, max. 300 words, plus max. 5 KEYWORDS)
KEYWORDS: Infection Prevention, Mathematical Modelling, Statistics, Epidemiology, Antibiotic Resistance

Antimicrobial resistance among bacteria is increasing worldwide, especially in hospitals. Hence, effective control strategies to prevent the spread of multidrug resistant pathogens (MDRP) are needed. Unfortunately, the epidemiology of MDRP is complex. One of the most important complicating factors is the inherent dependence between patients, i.e., the risk to acquire MDRP depends on the number of other patients being colonized with MDRP. Yet, this aspect has been neglected in the statistical analyses of almost all relevant studies performed so far, which raises doubts about reported causality between interventions and effects. Recently an algorithm (see [3]) was developed, that estimates the importance of different acquisition routes (cross-transmission and endogenous selection) from observational data while taking patient dependency into account. In this proposal, I aim

1. to incorporate additional relevant medical data into this algorithm. I will investigate how patient-specific variables (such as antibiotic use, severity of illness, and location) influence MDRP dynamics. These analyses will be performed with existing (and currently obtained) detailed longitudinal databases on MDRP, both from Dutch and foreign hospitals.
2. to develop statistical tools, based on [3], which do incorporate dependence. An important aspect is the development of goodness of fit tests to ascertain the quality of mechanistic transmission models.
3. to develop simulation models (as in [10]) to predict the effects of interventions. These simulation models will combine detailed structures and estimates of transmission and patient characteristics, as obtained in part 1. Based on insights obtained from these models, infection control interventions will be proposed that can then be empirically evaluated.

By analysing real-life data with tailor-made statistical tools involving new mathematical models, our understanding of MDRP epidemiology will be enhanced, the design and interpretation of clinical studies will be improved and we will generate evidence-based recommendations for controlling the spread of MDRP.

1d. NWO Council area
MW: 'Medische Wetenschappen' (Medical Sciences)

1e. Host institution (if known)
From September 2005 - September 2006, I worked as research fellow at the Department of Infectious Disease Epidemiology of Imperial College London. Progress in science often benefits from the blending of know how and in that spirit I intend to take advantage of previous experiences in new projects at the Mathematical Institute of Utrecht University and the UMCU. Moreover, my plan is to visit another top institute during the VENI period if the proposal is granted. For instance, the group of Prof. A.N. Pettitt, Queensland University of Technology, Brisbane, Australia or the group of Prof. M. Lipsitch, Harvard, Boston, USA.

Research proposal

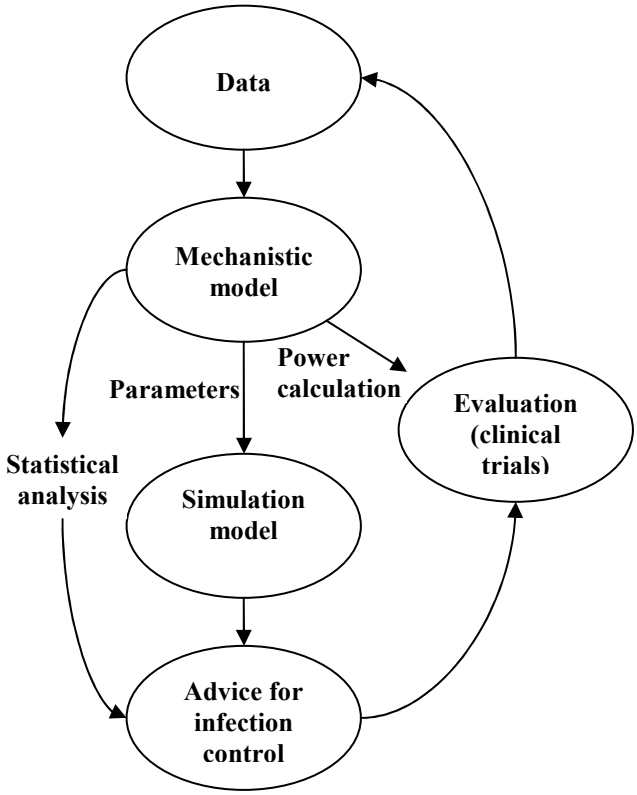
2. Description of the proposed research

(Use a maximum of 2000 words on no more than 4 pages, not including literature references (2e) and the utilisation paragraph (2f) if applicable.) 1995 words.

2a. Research topic

With a limited armentarium of antibiotics available, prevention of colonization and infection with MDRP becomes increasingly important. Since colonization may, as effective as infection, contribute to spread, infection control must be focussed on colonization rather than infection. The epidemiological characteristics of different MDRP (e.g., duration of the infectious period, relative importance of different routes of transmission, distribution on body sites) may differ, precluding uniform efficacy of specific intervention measures for all MDRP. For instance, when cross transmission (i.e., exogenous route) through health care workers or the environment is important, improved hygienic measures may be effective. If, however, the endogenous route (i.e., selection of already pre-existing MDRP due to antibiotic use or de novo resistance development) is more important, reduction of selective antibiotic pressure is more appropriate.

Many different interventions have, repeatedly, been evaluated in hospitals. Most of these studies used a quasi-experimental study design (typically a before-after study). The tenet underlying my research proposal is that the analytical tools used for determining the effects of these interventions have been inappropriate. Patient dependency is characteristic for any infectious disease, and certainly also for MDRP; the risk for a susceptible patient to acquire MDRP increases when the number of colonized neighbouring patients increases. Almost all clinical intervention studies have used statistical tests (such as χ^2 or Student's t-test) which ignore this dependence. Differences between the baseline and intervention period, considered to be significant according to these tests, need not imply causality between intervention and outcome. (With cross transmission accounting for 80% of the acquisitions, the likelihood to obtain a statistically significant difference between two periods can be 40% in absence of interventions, see [1]). Furthermore, power-analyses, applied in the design of clinical trials, neglect this dependence, yielding many studies underpowered to obtain statistically significant results.



Schematic representation of the interplay between the components of this proposal

The aim of this proposal is to develop statistical tools that take dependency into account. These tools will be applied to analyse the effects of clinical trials. Parameters estimated by these tools, may next be used as input for simulation models to predict the impact of

intervention measures. So far, statistical work for infectious diseases has mainly focussed on rather theoretical issues without much concern for applicability to the analysis of data of clinical trials. For example, typically, perfect observation of the spread is assumed. Similarly, most simulation models that are used to investigate the impact of intervention measures make use of rather caricatural models. These models may provide insight in how interventions change dynamics, but qualitative predictions typically lack robustness due to many simplifying assumptions. Especially the neglect of heterogeneity among patients is restrictive.

The work proposed here, continues the work I have performed in the NWO-CLS project "Data driven multi level models of infectious diseases" [2]. Within that project, an algorithm [3] was developed to estimate the importance of different acquisition routes of nosocomial MDRP by using longitudinal data only. In contrast to other approaches [4-9], this algorithm uses all available data (period of stay, results and moments of culturing), where others assumed a fixed number of occupied beds and ignored the actual distribution of the duration of stay and used exponentially distributed lengths of stay instead. Moreover, as patients are not individually represented in these models, culture results cannot be used on an individual patient level. As a result, dependence in culture results (once colonized, the likelihood of persistent colonization is high) is ignored as well. For all these reasons, our approach of including individual patient data will improve the accuracy substantially.

2b. Approach
The work will focus on estimation of parameters in a mechanistic model for the transmission dynamics of MDRP in hospital settings. This mechanistic model will incorporate all relevant structures, acquisition routes and individual patient characteristics (e.g., antibiotic use). For each pathogen of interest, model parameters will be estimated. The main advantages of this approach are that the parameters have a clear interpretation and that they can be estimated while taking dependencies into account.

The algorithm of [3] allows for direct maximum likelihood estimates of the importance of different acquisition routes (exogenous and endogenous) for hospital units of typical size. I prefer to stay within this framework to avoid additional assumptions. When there is a considerable amount of missing data or when the culture results are not 100% reliable, this approach may not be feasible anymore for numerical reasons. In these cases I intend to use Monte Carlo Markov Chain methods.

I will extend the algorithm introduced in [3] into two directions: First by incorporating relevant medical data, and second by developing new statistical tools.

Incorporation of medical data:
I will explicitly incorporate patient-specific daily antibiotic use into the model to investigate to what extent colonized patients become more infectious and to what extent uncolonized patients become more susceptible for endogenous and exogenous acquisition of MDRP when they receive or have received antibiotics?
I also aim to determine how severity of illness (such as APACHE II) explains differences in susceptibility for MDRP pathogen acquisition. Similarly, I will investigate the role of patient localisation in a ward and its relation to the interaction with health care workers.

New statistical tools
Conclusions about the relevance of these factors (and interventions affecting them) should be based on solid statistical tests and, hence, the previous issues are very much related to extensions in the second direction.

Within the framework of [3], I aim to develop a power analysis that takes both dependency and culture frequency into account. The latter is essential, because the colonization status of a patient is frequently unknown; the colonization status is not monitored continuously and culture or genotyping methods are not 100% accurate. I will try to generalize theoretical results with regard to the asymptotic speed of convergence of parameter estimates in case of independence and I will compare results with simulation results.

Furthermore, I aim to develop a goodness of fit test to ascertain how well the mechanistic transmission model explains the data. When the maximum likelihood estimators suggest that cross transmission is absent and patients are independent, standard goodness of fit tests can be used. When cross transmission is relevant though, no standard tests exist. Numerical methods based on simulating a unit with the same characteristics as the real unit may be part of the solution. However, how to compare the simulated data with the real data (e.g., based on the likelihood of the data) is not clear, as there can be huge differences in likelihood between simulations due to stochastic fluctuations. Note that even with suboptimal goodness of fit, such a mechanistic model may reflect reality much better than models which neglect dependency.

The translation of statistical results to medical conclusions also requires elaboration. Currently, the optimal method to compare estimates of transmission parameters pertaining to, respectively, a baseline and intervention period is unknown. When the mechanistic model incorporates only one acquisition route, comparison of the two periods is relatively straightforward (although theoretical problems with regard to deriving confidence intervals still exist; see [3]); the more reduced the transmission parameter, the more effective the intervention. However, when the mechanistic model has several acquisition routes (which occurs in real life), no standard ordering of sets of transmission parameters exists and it is not obvious how to interpret results when one parameter value increases and another decreases after an intervention.

The third component of this proposal addresses the design of efficient infection control strategies, see e.g., [10]. This is far from an easy task, as no unique definition of an optimal control strategy exists. Draconic measures may be efficient in controlling spread, but may be considered too expensive or unethical, whereas cheaper and/or more patient-friendly measures may be inefficient in the long run. The optimal strategy may depend critically on the weight of several components, such as:

- the decrease in prevalence of colonization due to the intervention measures.
- the decrease in attributable morbidity or mortality.
- the time scale needed to observe improvements.
- Constraints which limit the available options, such as:
    - finances
    - are the interventions feasible with the current staff or is there a need for more (specialized) personnel?
    - the number of isolation beds available

I will develop simulation models that mimic the dynamics of MDRP in units, hospitals and even countries. These simulation models will combine estimates of acquisition rates in different rooms/units, antibiotic use and other patient characteristics with detailed information of the patient flow between units and the extramural community (typically available within databases of hospitals). This will make qualitative predictions of the effect of (combinations of) intervention measures more robust. In addition, the effect of targeted approaches can be evaluated. For instance, the current Dutch infection prevention guidelines for methicillin-resistant *Staphylococcus aureus* (MRSA) [11] are similar for all units, but stringent measures within high-risk units (e.g., haemodialysis

units, ICUs) and less restrictive measures in the other wards of the hospital, could be equally effective, while less effort and money is required to enforce these measures.

2c. Innovation

The strength of this proposal is that it provides a bridge between the medical and the mathematical world. The research will focus on correct statistical use of medical data, where we, from the very beginning, keep the nature of the available data in mind to optimise their use. More detailed knowledge of how antibiotic use and heterogeneity influence the dynamics of MDRP will allow for more reliable simulation models which can assist in the design of efficient intervention measures. Mathematical modelling is frequently used for infections in large populations (such as pandemic flu). Our research group is one of the few in the world developing these powerful techniques for much smaller populations with completely different epidemiological characteristics.

From a long term perspective, the key point of the proposal is to enable the applicant to complete the transformation from a mathematically oriented theoretical physicist into an expert in the quantitative epidemiology of infectious diseases. Without any doubt, such experts are needed to safeguard public health in the future. The applicant is eager to act as organising centre for the interdisciplinary collaboration in this area in the Netherlands.

2d. Plan of work

An important feature of this work will be the collaboration of health care specialists and mathematicians/modellers. Apart from the applicant (and several, both medical and mathematical, PhD-students), the research group will consist of:

Name	Speciality	Institute
Prof. dr. O. Diekmann	Mathematical modelling (MM)	Mathematical Institute Utrecht University (UU)
Prof. dr. M.J.M. Bonten	Molecular Epidemiology of Infectious Diseases (MEID)	University Medical Center Utrecht (UMCU)
Dr. J.P. Trapman	MM	UMCU/UU
Dr. R. Willems	MEID	UMCU

During interdisciplinary meetings, relevant medical questions will gradually be formulated in such a way that they become mathematical problems. The consequences of mathematical simplifications for the medical interpretation and the mathematical consequences of incorporating additional structures will be discussed, together with the possibilities to test the relevance of these structures with data. For this, many prospectively collected databases of unique and very detailed (intervention) studies are available. Within the UMCU: longitudinal (point-)prevalence studies of ampicillin-resistant enterococci, third-generation-cephalosporin-resistant Enterobacteriaceae and a recently finished multi-centre study of selective digestive decontamination with >125000 culture results during >70,000 patient days of about 6000 ICU patients. Detailed databases are also available via international collaborations (see section 4.g) and these will provide insight in the dynamics of MDRP with (still) low prevalence in the Netherlands, e.g. (CA)-MRSA and vancomycin-resistant enterococci from Chicago, and of antibiotic policy interventions for *Pseudomonas aerigunosa*, Extended Spectrum *β*-Lactamase producing Enterobacteriaceae, MRSA, gentamicin-resistant *Klebsiella pneumoniae* and amikacin-resistant *Acinetobacter spp* from Ho Chi Minh City, Vietnam.

The first 18 months, I will investigate the influence of antibiotics, and other factors related to heterogeneity, on transmission dynamics. The construction and evaluation of simulation models will be concentrated in the second 18 months, as the results of the data analysis serve as input. A formal timetable for the statistical issues is unreliable, as the technical problems are often unforeseeable, but I am convinced that I will succeed with that task within the time frame of this proposal.

2e. Literature references

[1] S. Nijssen, M.C.J. Bootsma, M.J.M. Bonten. Potential confounding in evaluating infection control interventions in hospital settings: changing antibiotic prescription. Clin Infect Dis 2006;43:616–23.

[2] NWO-program on Computational Life Sciences: Data driven multi level models of infectious diseases. Grant nr. 635.100.002. Website: http://www.math.uu.nl/people/boldin/nwo/

[3] M.C.J. Bootsma, M.J.M. Bonten, S. Nijssen, A.C. Fluit, O. Diekmann. An Algorithm to Estimate the Importance of Bacterial Acquisition Routes in Hospital Settings. Am J Epidemiol Accepted. Preprint available at http://www.math.uu.nl/people/bootsma/publicaties.html/

[4] I. Pelupessy, M.J.M. Bonten, O. Diekmann. How to assess the relative importance of different colonization routes of pathogens within hospital settings. Proc Natl Acad Sci USA 2002;99:5601–5.

[5] B. Cooper, M. Lipsitch. The analysis of hospital infection data using hidden markov models. Biostatistics 2004;5:223–37.

[6] M. Forrester, A.N. Pettitt. Use of stochastic epidemic modeling to quantify rates of colonization with methicillin-resistant Staphylococcus aureus in an intensive care unit. Infect Control Hosp Epidemiol 2005;26:598–606.

[7] M.L. Forrester, A.N. Pettitt, G.J. Gibson. Bayesian inference of hospital-acquired infectious diseases and control measures given imperfect surveillance data. Biostatistics (2006) doi:10.1093/biostatistics/kxl017.

[8] E.S. McBryde, A.N. Pettit, D.L. McElwain. A stochastical model of methicillin-resistant Staphylococcus aureus transmission in an intensive care unit: Predicting the impact of interventions. J Theor Biol. 2007; doi:10.1016/j.jtbi.2006.11.008.

[9] R.T. Mikolajczyk, U. Sagel, R. Bornemann, A. Krämer, M. Kretzschmar A statistical method for estimating the proportion of cases resulting from cross-transmission of multi-resistant pathogens in an intensive care unit. J Hosp Infect. 2007;65:149–155.

[10] M.C.J. Bootsma, O. Diekmann, M.J.M. Bonten. Controlling of methicillin-resistant Staphylococcus aureus: Quantifying the effects of interventions and rapid diagnostic testing Proc Natl Acad Sci USA. 2006;103:5620-5625.

[11] Werkgroep Infectie Preventie. MRSA, ziekenhuizen. WIP richtlijn.

2f. Utilisation paragraph: Only required for proposals to be submitted to Technical Sciences (STW), see Notes.

Cost estimates

3a. Budget

	2008	2009	2010	(2011)	TOTAL
Staff costs: (in k€)	48	65	67	17	197
Applicant	48	65	67	17	197
Support staff	-	-	-	-	-
Non staff costs: (k€)	4	3	3	1	11
Equipment	2	-	-	-	2
Consumables	-	-	-	-	-
Travel and subsistence	2	3	3	1	9
Other	-	-	-	-	-
TOTAL	52	68	70	18	208

3b.Indicate the time (percentage of fte) you will spend on the research
90% (10% teaching duties)

3c. Intended starting date
(dd/mm/yyyy) 01/04/2008

3d. Have you requested any additional grants for this project either from NWO or from any other institution? no

Curriculum vitae

4a. Personal details

Title(s), initial(s), first name, surname:	M.C.J. (Martin) Bootsma, PhD
Male/female:	Male
Date (dd/mm/yyyy) and place of birth:	18/12/1977, Almelo, The Netherlands
Nationality:	Dutch
Birth country of parents:	The Netherlands

4b. Master's ('doctoraal')

- University/College of Higher Education: Utrecht University
  Date (dd/mm/yyyy): 29/01/2001
  Main subject: Theoretical Physics (cum laude)

- University/College of Higher Education: Utrecht University
  Date (dd/mm/yyyy): 29/01/2001
  Main subject: Mathematics

4c. Doctorate

University/College of Higher Education:	Utrecht University
Starting date (dd/mm/yyyy):	01/02/2001
Completion date (dd/mm/yyyy):	23/05/2005
Supervisor ('Promotor'):	Prof. dr. O. Diekmann (UU) Prof. dr. M.J.M. Bonten (UMCU)

Title of thesis: Mathematical studies of the dynamics of antibiotic resistance
(available at: http://igitur-archive.library.uu.nl/dissertations/2005-0526-201427/index.htm

4d. Work experience since graduating

(per appointment: fte, tenured term ('vast') / fixed-term ('tijdelijk').

01/04/2005 – Present:	Postdoc (1.0 fte, fixed term of three years) in the NWO CLS 635.100.002 project: Data driven multi level models of infectious diseases.
09/2005 – 09/2006:	Research fellow at the Department of Infectious Disease Epidemiology of Imperial College, London, UK under guidance of Prof. Neil M. Ferguson

4e. Man-years of research

(see Notes)
2 years and 1 month (per 01/05/2007) as postdoc

4f. Brief summary of research over last five years

(210, maximum 250 words)
During my four years as PhD-student and two years as postdoc I have been working on mathematical models to describe and quantify the epidemiology of infectious diseases. The main focus has been on the spread of nosocomial MDRP, with the exception of the year I spend as research fellow at the department of infectious disease epidemiology at Imperial College London. During this year I have studied, together with Prof. Neil Ferguson, the effect of interventions, like closure of schools and churches, banning of mass gatherings and mandated mask wearing, which were implemented in U.S. cities during the 1918 Spanish influenza epidemic (see publication **5**).

One branch of research was devoted to the processing of data from clinical studies while taking dependency between patients into account. I developed an algorithm to estimate the importance of different acquisition routes in hospital settings by using longitudinal data only (without the need of time-consuming, expensive and sometime unreliable genotyping data). The other branch was focussed on the construction and analysis of mathematical models for the spread of nosocomial pathogens. The main aim was to predict the effect of several intervention measures within hospitals. A special focus was to quantify the effect of the individual components of the Dutch Search & Destroy policy for MRSA.

4g. International activities
From September 2005 till September 2006 I worked as a research fellow at the department of infectious disease epidemiology of Imperial College London were I have been working with Prof. Neil Ferguson. I am also collaborating with Prof. Bob Weinstein and dr. Bala Hota in Chicago (John H. Stroger, Jr, Hospital of Cook County) and dr. Constance Schultsz, (Oxford University Clinical Research Unit Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam).

4h. Other academic activities

4i. Scholarships and prizes
GSK ICAAC-2005 Award (€2,500) for the best presentation by a Dutchman at the Interscience Conference on Antimicrobial Agents and Chemotherapy 2005 in Washington DC, USA, December 2005.

List of publications

5. Publications:
Key publications, which are directly relevant to the proposed research, are marked with an S.

- Average impact factor for own field (only compulsory if your proposal is to be submitted to Medical Sciences, see Notes)
There is huge difference in impact factors between the medical and the mathematical field. The average impact factors are 0.95 for applied mathematics and 1.99 for infectious diseases. Articles with medically relevant conclusions will be (and have been) submitted to medical journals, whereas those addressing methodological and mathematical issues will be published in more specialized journals, with inherently, a lower impact factor.

- International (refereed) journals (include impact factor of journal, only compulsory if your proposal is to be submitted to Medical Sciences, see Notes)

1 M. Bonten, J. Kluytmans, A. de Smet, M. Bootsma, A. Hoes. Correspondence: Selective decontamination of digestive tract in intensive care. Lancet, 362:2118-2119, 2003. Impact Factor (2005) 23.407 Rank 3 (Category: general medical journals).

S **2** Controlling methicillin-resistant Staphylococcus aureus: Quantifying the effects of Interventions and rapid diagnostic testing. M.C.J. Bootsma, O. Diekmann, and M.J.M. Bonten (2006). Proc. Natl. Acad. Sci. USA 103, 5620-5625. Impact Factor (2005) 10.231. Rank 3/48 (Category: Multidisciplinary Sciences.)

3 S. Nijssen, M.C.J. Bootsma, M.J.M. Bonten. Potential confounding in evaluating infection control interventions in hospital settings: changing antibiotic prescription. Clinical Infectious Diseases, 43:616-623, 2006. Impact Factor (2005) 6.51 Rank 3 (Category: infectious diseases).

4 M.C.J. Bootsma, O. Diekmann. Comment on ”linking population level models with growing networks: A class of epidemic models”. Phys. Rev. E, 74:018101, 2006. Impact Factor (2005) 2.418.

5 M.C.J. Bootsma, N.M. Ferguson. The effect of public health measures on the 1918 influenza pandemic in US cities. Proc. Natl. Acad. Sci. USA. Published online Apr 6, 2007, doi:10.1073/pnas.0611071104; Impact Factor (2005) 10.231. Rank 3/48 (Category: Multidisciplinary Sciences.)

S **6** M.C.J. Bootsma, M.J.M. Bonten, S. Nijssen, A.C. Fluit, O. Diekmann. An Algorithm to Estimate the Importance of Bacterial Acquisition Routes in Hospital Settings. Am J Epidemiol Accepted. Impact Factor (2005) 5.068 Rank 2/99 (Category: Public, Environmental and Occupational Health). Preprint available at: http://www.math.uu.nl/people/bootsma/publicaties.html/

- National (refereed) journals

- H. Grundmann, M. Bootsma. Predicting the success of preventive measures in infection control using mathematical models. Nederlands Tijdschrift Voor Medische Microbiologie, 12:14-16, 2005.

- Abstracts/Conference reports

- S. Nijssen, M. Bootsma, M. Bonten, A. Hoepelman. Dynamics of colonization with third generation cephalosporinresistant enterobacteriaceae in icu patients. 2002. abstract no: 2179 ICAAC.

- M. Bootsma, M. Kooistra-Smid, H. Verburgh, O. Diekmann, M. Bonten. A mathematical model for the transmission of s. aureus (sa) in a burn wound center. 2002. abstract no: K106, 42nd ICAAC.
- M. Bootsma, M. Bonten, I. Pelupessy, A. Hoepelman, O. Diekmann. Nosocomial infection (ni) and length of stay (los) in intensive care: A simple observation on cause and effect. 2002. abstract no: K-656, 42nd ICAAC.
- M.C.J. Bootsma, O. Diekmann, M.J.M. Bonten. How to control interhospital spread (ihs) of multi-drug resistant pathogens (mdrp): Preditions from a mathematical model. 2003. abstract no: K1102.
- K. Schurink, M. Bootsma, M. Bonten. Early- and late-onset ventilatorassociated pneumonia (vap): Relevance of definition. 2003. abstract no: K-452 43rd ICAAC.
- M.C.J. Bootsma, O. Diekmann, M.J.M. Bonten. A mathematical model (mm) for the effects of selective digestive decontamination (sdd) on antibiotic resistance. 2003. abstract no: K698, 43rd ICAAC.
- S. Nijssen, J. Top, R. Willems, M. Bootsma, A. Fluit, M. Bonten. Prospective validation of a mathematical model to determine relative importance of different acquisition routes in intensive care units. 2003. abstract no: K-124, 43rd ICAAC.
- M.C.J. Bootsma, O. Diekmann, M.J.M. Bonten. Estimating transmission parameters for infectious diseases in small hospital units. In Design and Analysis of Infectious Disease Studies, Mathematisches Forschungsinstitut Oberwolfach. Report No. 49/2004.
- A. van der Zee, M. Bootsma, R. Radersma, J. Nelson, A. Buiting. A comparision of mathematic modelling and molecular genotyping for assesment of transmission routes of escherichia coli among icu patients. 2005. abstract no: 16B, IMMEM7.
- M.C.J. Bootsma, O. Diekmann, M.J.M. Bonten. Efficacy of search and destroy (s&d) in high endemic mrsa settings (hes): Results from a simulation model (sm). 2005. abstract no: K548/419, 45th ICAAC.
- M.C.J. Bootsma, O. Diekmann, M.J.M. Bonten. Quantitative effects of individual measures of search and destroy (s&d) of mrsa. 2005. abstract no: K549/420, 45th ICAAC.
- M.C.J. Bootsma, O. Diekmann, M.J.M. Bonten. Pros and cons of rapid diagnostic testing (rdt) for controlling mrsa. 2005. abstract no: K550/421, 45th ICAAC.
- M.C.J. Bootsma, B. Hota, O. Diekmann, R.A. Weinstein, M.J.M. Bonten. A mathematical model to determine the growth rate of ca-mrsa and options for control. 2006. abstract no: K-1680.

- Invited talks

- Het effect van nosocomiale verspreiding op het resistentieniveau in de extramurale populatie. April 24, 2003. SWAB Symposium, Utrecht, the Netherlands.
- Infections in the hospital: Relative importance of infection routes. May 19, 2005. Staff Colloquium Mathematical Institute Utrecht University.
- Controlling MRSA: Now and in the future. May 11, 2006. HPA London, UK seminar series.
- Estimating transmission parameters for infectious diseases in small hospital units. August 7, 2006. Kolloquium Medizinische Biometrie, Freiburg, Germany.
- MRSA: Options for control. November 9, 2006. Warwick Business School, University of Warwick, Coventry, United Kingdom.

- Mathematical models for transmission and control of MRSA. November 10, 2006. MRSA Symposium Brighton, United Kingdom.
- Three aspects of the spread of antibiotic resistance: hospital re-entry, multiple acquisition routes, multiple colonization sites. April 13 2007. Workshop on antibiotic resistance, Kräftiket, Stockholm, Sweden.

Signature

I hereby declare that I have completed this form truthfully:

Name: Martin Bootsma

Place: Utrecht

Date (dd/mm/yyy): 01/05/2007

Please submit the application to NWO in electronic form (pdf format is required!) using the Iris system, which can be accessed via the NWO website (www.nwo.nl/vi).

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  (to be sent by post, optional for Veni during the application procedure)
- ☐ **Address list of 'non-referees'**
  (to be sent by post before the submission deadline, optional for all applicants, maximum 3 names, see Notes)

1st Veni application

Name of applicant:	Martinus Christoffel Jozef (Martin) Bootsma
Place:	Utrecht
Date:	25/04/2007
Postal address:	Mathematical Institute, Utrecht University Budapestlaan 6, P.O.box 80010, 3508 TA Utrecht, The Netherlands

NWO Council area: MW

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