Understanding the Spread of Antibiotic Resistant Pathogens in Hospitals: Mathematical Models as Tools for Control

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As microorganisms become more resistant to antimicrobial agents, effective infection control measures will become increasingly important. However, despite multiple studies on infection prevention, few data exist on the quantitative effects of the individual aspects of infection control strategies. The combination of epidemiologic surveillance, molecular genotyping, observational studies on compliance, and mathematical modeling may improve our ability to determine the quantitative effects of individual infection control measures. This may help to design more effective infection control programs. In this study, we review several of the models that have been published and speculate on the usefulness of mathematical modeling for improving the prevention of infection.

The emergence of antibiotic resistance is considered by many to be one of the most important threats to human health in the 21st century [1]. Bacteria such as vancomycin-resistant enterococci (VRE) and glycopeptide-intermediate sensitive Staphylococcus aureus present hospitals with the prospect of a “post-tantibiotic era,” with few if any therapeutic antimicrobial agents remaining effective. Besides difficulties in treatment, multiresistant pathogens seem to have a remarkable ability to be transferred from patient to patient. For example, the presence of the variant esp gene has been associated with hospital outbreaks of VRE [2]. Limited therapeutic options mean that prevention will become increasingly important, thereby bringing the implementation of effective infection control strategies to the forefront.

A considerable body of clinical research has been dedicated to the study of infection control practices. It has been demonstrated repeatedly that compliance with hand disinfection by health-care workers, generally accepted as the cornerstone of infection prevention, is low, and that nurses are more compliant than physicians [3]. Although improved compliance has been associated with a decreased incidence of nosocomial infections [4], sustaining improvements in compliance seems to be very difficult. Furthermore, understaffing and selective antibiotic pressure have been associated with increased incidences of nosocomial infections and the occurrence of hospital outbreaks [5, 6]. Outbreaks are usually combated with a package of infection control measures, which may include education, improved staffing levels, improving compliance, changing antibiotic policies, and enforcement of barrier precautions. One downside to this multifaceted approach is that the precise impact of any single measure, whether successful or unsuccessful, cannot be determined [7]. Despite a multitude of studies, there have been limited quantitative measures of the practical efficacy of infection control practices in either epidemic or endemic settings.

The use of a theoretical framework to conceptualize the underlying processes and its subsequent formulation by use of mathematical modeling may be of help in the quantification of the transmission process and subsequent effects of infection control practices. Mathematical modeling has a particularly successful record in aiding understanding of the epidemiology of infectious diseases, especially in the description of the transmission dynamics of diseases ranging from measles and per-
tussis to gonorrhea and in the prediction of the effects of public health interventions such as treatment and vaccination on these dynamics [8]. Few physicians, however, feel comfortable in applying concepts from the mathematical sciences (in which cause and effect are assumed) to clinical problems, relying instead on the statistical sciences for the elucidation of association. This discomfort has led to a gap between clinical practice and the theoretical sciences. Recently, the first attempts have been made to apply theoretical techniques to the investigation of infection control strategies, with particular attention being paid to intensive care units (ICUs) [9–12]. Herein we describe several of the earliest theoretical models proposed and speculate on the potential role of mathematical modeling in infection control.

**MATHEMATICAL MODELING: THE CONCEPT**

Mathematical modeling provides a means of exploring complex relationships among interdependent variables. It necessarily involves the simplification of the system being described but forces the modeler to write down, in a precise manner, a framework of interactions (hypotheses). For example, the number of factors that influence the acquisition of an antibiotic-resistant pathogen in an ICU is likely to be enormous: patient demographics, rates of admission and discharge, reason for admission, staffing levels, severity of illness, antibiotic usage patterns, hand-washing compliance, nursing shift, and so on. Addressing this level of complexity may, however, be unnecessary, because only a subset is likely to be of prime importance. Deciding which factors and how they should be quantified is where clinical medicine meets mathematics.

Once the biological and epidemiological processes in a model are specified, the predictions of the model are assessed by use of 2 complementary techniques. If models are not too complex, it is often possible to make general statements about their behavior that do not depend on specific values of parameters. The most famous such result in community-acquired infections is that an infection can spread and persist in a community if its basic reproductive number (the number of secondary cases caused by a single infectious case in an uninfected population) exceeds 1 [8]. The advantage of this “analytical” approach is its generality; the disadvantage is that it can only describe certain aspects of the behavior of a model. A complementary approach is the numerical simulation of a model, in which a particular scenario with specific values for each parameter—admission rate, length of stay, transmission rate, effect of antibiotics, etc.—are assumed, and the model is allowed to run, simulating the transmission in an ICU with those parameter values. This simulation approach gives more detailed information about the transmission model, but the information is (strictly speaking) only applicable to particular parameter values chosen.

Most of the models described below are deterministic, in that the ordinary differential equations used give predictable behavior from a specified starting condition. Chance events are not taken into account in model formulation. In small populations such as ICUs, significant fluctuations in the incidence and prevalence of colonization and infection will happen just by chance. For example, 1 additional case in an 8-bed ICU increases the prevalence of infection by 12.5%! Deterministic models must therefore be interpreted as a first approximation of what will happen in any particular ICU. Even when a model correctly describes the epidemiology, a single observation may bear no resemblance to the analytic behavior. To capture the element of chance in transmission dynamics within an ICU, the analytic models described must be evolved stochastically, with events formalized in the analytical framework and simulated randomly with event rates prescribed by the model. In this way, it is possible to see the range of outcomes expected in real situations, accounting for the effect of random fluctuations. We describe some such models below.

**METHICillin-RESISTANT S. AUREUS IN THE ICU**

Sébille et al. [11] proposed a model of an ICU in which patients are admitted either colonized or noncolonized with an antibiotic-resistant pathogen like methicillin-resistant *S. aureus*. Patients and staff members interact through hand contacts, which are either direct from staff member to staff member or indirect from patient to patient via a staff member or via contaminated equipment. An outbreak was simulated by the admission of patients colonized with the resistant pathogen. Colonized staff members clear colonization at some rate—more rapidly if they comply with hand-disinfection procedures. The changes in time of the numbers of patients and staff members being colonized with the resistant strain are described by use of differential equations and combine rates of contamination, colonization clearance, and admission of colonized patients. Furthermore, patients can receive 2 types of antibiotics: a topical and a systemic agent. The topical antibiotic (for example, mupirocin), is given to patients colonized with a mupirocin-sensitive strain, whereas the systemic agent (for example, vancomycin), is given to patients colonized with a mupirocin-resistant strain.

Individuals are counted in 1 of 3 compartments: noncolonized individuals, individuals colonized by a mupirocin-resistant strain, and individuals colonized by a mupirocin-sensitive strain. Patients are assumed not to be colonized by a vancomycin-resistant strain.

Analysis of the model showed that the most important determinant of transmission was the number of patients being
colonized by strains transmitted from health-care workers \( (\beta_{sp}, \) the mean annual number of patients colonized by 1 colonized staff member). Under the assumption of a fixed admission prevalence of 10% (5% with mupirocin-resistant and 5% with mupirocin-sensitive strains), the total percentage of colonized patients increased from 18%, without transmission \( (\beta_{sp} = 0), \) to almost 50% when \( \beta_{sp} = 50. \) Interestingly, increasing rates of compliance with hand disinfection showed little effect on the total prevalence of patient colonization. With 10% admission prevalence and \( \beta_{sp} = 30, \) once endemic, 30% of the patients are predicted to be colonized without any hand disinfection. This endemic prevalence decreases to 22% of patients with 40% compliance and 20% of patients with 60% compliance. Subsequently, the effects of different antibiotic policies were determined. Patients with mupirocin-sensitive strains received mupirocin, which is assumed to clear colonization in 80% of cases. Patients colonized with the mupirocin-resistant strain received vancomycin, which cleared only 30% of cases. There was no marked impact on patient colonization rates, either when antibiotics were used simultaneously or alternatively. Finally, only by curtailing the admission of colonized patients was the pathogen rapidly eradicated.

**VANCOMYCIN-RESISTANT ENTEROCOCCI IN THE ICU**

In a second model, by Austin et al. [9], the transmission of nosocomial pathogens was described by use of a microepidemiologic framework analogous to those of vectorborne diseases, which is basically the same approach as that of the previous model (figure 1). If health-care workers are viewed as vectors and patients as definitive hosts, the model is similar in structure to that used in the study of malaria (i.e., Ross-MacDonald equations). In this instance, the model was specifically applied to the colonization dynamics of VRE, and the predictions of the model were compared with epidemiologic observations in an ICU in which colonization with VRE was endemic [13]. Again, colonized and noncolonized patients and health-care workers were compartmentalized and their changes in number expressed as a set of differential equations. Counting the 7 possible events, the potential effects of infection control are clearly visible in figure 1. One difference between this model and that described by Sébille et al. [11] is the inclusion of cohorting (mixing) as a means of infection control. The level of cohorting of health-care workers was defined as the probability that, after a health-care worker–patient contact, the next contact would be with the same patient. If the nurse-patient ratio is 1:1, each nurse could (in principle) have contact with only a single patient, and transmission of pathogens would not be possible. In reality, however, nurses may be primarily dedicated to a single patient but frequently assist other nurses. Moreover, physicians usually take care of (and contact) all patients in the unit.

**THE BASIC REPRODUCTIVE NUMBER: \( R_0 \)**

The transmission dynamics of VRE are characterized by the basic reproductive number, \( R_0, \) defined as the average number of secondary cases of colonization generated by 1 primary case of VRE colonization in a VRE-free ICU without any infection control. Highly transmissible organisms will have a large \( R_0, \) which may reflect both the colonizing ability of a pathogen (bacterial transmissibility) and the organization of the ICU (contact rates, etc.). If \( R_0 > 1, \) each colonized patient will (on average) generate a further case and an epidemic can ensue (with probability \( 1 - 1/R_0 \)). Eventual endemic persistence is
unlikely without colonized admissions because of the small number of patients involved (unless $R_0$ is much greater than 1), and the epidemic will stutter to extinction.

**$R_0$ AND INFECTION CONTROL**

Infection control practices serve to reduce the basic reproductive number to an effective reproductive number, $R_e$, which is a measure of in situ transmission. Barrier precautions such as hand disinfection and the use of gloves and gowns serve to reduce the likelihood that health-care workers will become (and remain) contaminated. If the probability of compliance is $p$ and efficacy of clearing contamination is assumed to be 100%, the effective reproductive number with this measure will change to $R(p) = (1 - p)R_e$. With 100% compliance, $R(p) = 0$, and there can be no transmission. There is a critical threshold for compliance to decrease the effective reproductive number below unity, which is $p_c = 1 - 1/R_e$. This threshold equation implies that compliance must increase to maintain effective infection control when $R_0$ increases. A compliance of 40% may be sufficient for control of pathogen A but insufficient for pathogen B. Observed compliance in ICUs seldom exceed levels of 40%-50% and have repeatedly been reported to be even lower.

**COHORTING**

Because 2 contacts are needed for transmission of pathogens (bacteria must move from patient to health-care worker and vice versa), the per capita contact rate appears as a squared quantity in the expression for the basic reproductive number (not shown). Changes in mixing patterns can potentially have large effects. In the VRE model, health-care workers were subdivided into medical staff (who are not cohorted) and nursing staff (who have a probability, "$q$," of having cohorted contacts). In other words, $q$ is the probability that the next contact will be with the same patient. With cohorting, both the contact rate per health-care worker and the effective number of health-care workers change such that the effective reproductive number is given by $R(q) = R_e(1 - qn)$, where $n$ is the proportion of nurses among the total staff. Preliminary observations suggest that cohorting of nursing staff in different ICUs is ~80% (M.J.M.B. and D.J.A., unpublished data). This is in broad agreement with clinical experience: effective isolation of patients (extreme cohorting) and cohorting of health-care workers to patients can prove to be an infection-control measure.

**ANTIBIOTIC USE**

Finally, changes in antibiotic prescription may also serve as an infection-control measure. In the model, it was assumed that certain antibiotics create an increased relative risk for colonization ($e$) after a contact with a contaminated health-care worker. This assumption is in contrast to models of resistance (see below), because it is not specific for a bug-drug combination. Moreover, the duration of antibiotic therapy has the potential to increase the risk for colonization, because patients are less protected by their own flora, which increases the numbers of potentially dangerous contacts. The amount of antibiotic exposure was expressed as the proportion of days in ICU that a patient received antibiotics ("$a$"). Combining both factors increases the probability per contact of colonization by a factor of $1 + ae(e - 1)$ and the effective reproductive number, $R_e$, accordingly.

**COMBINED MEASURES OF INFECTION CONTROL**

As has already been stated, infection-control measures are typically multifaceted, and their effects must be accommodated accordingly. Combining the effects of hand disinfection and cohorting, the effective reproductive number for in situ transmission takes the form $R(p,q) = (1 - p)(1 - qn)R_e$. Control of transmission requires $R(p,q) < 1$, which, of course, depends on $R_e$. The relationship between different levels of compliance and cohorting when $R(p,q) = 1$ is depicted in figure 2. Reducing the proportion of days that patients receive selective antibiotics makes infection control even more effective, although the effect is less noticeable when $R_0$ is large. The results of stochastic simulations of the model are remarkably similar.
to those reported by Sébille et al. [11]. Hand disinfection has an important effect on infection prevention, but the effects are most profound between 0 and ~50% compliance. An increase from 40% to 60% (which would require concerted effort) will only have limited additional benefit. Intuitively, one can imagine that only a few noncompliant health-care workers will be enough to maintain transmission.

COMPARING THE MODEL TO REAL OBSERVATIONS

The predictions of the model from Austin et al. [9] are compared with epidemiological observations made in a medical ICU in which colonization with VRE was endemic. Observations and molecular typing provided precise data regarding demographics. Admission rates of patients with (15%) and without (85%) VRE, acquisition rates of VRE, proportions of acquisition being the result of cross-acquisition (80%), compliance with hand disinfection (50%), the endemic prevalence of colonization (36%), and lengths of stay of patients with and without VRE were determined. The level of cohorting of nursing staff was assumed to be 80%. The calculated effective reproductive number \( R_0 \) was estimated to be 0.69, which implies that transmission alone cannot sustain VRE in the ICU. This means that the 15% of patients admitted already colonized stabilized endemicity, thwarting the efforts of sustained and reasonable infection control measures. Subsequently, \( R_0 \) was determined from the inverse relationship, \( R_0 = R(p,q) / (1 - p)(1 - qn) \), to be 3.8. This finding implies that without any infection control measures, the predicted endemic prevalence of VRE would have been 79% (including colonized admissions). The effects of the infection control measures, therefore, have reduced the prevalence from a potential 79% to the observed 36% and reduced \( R_0 \) by 82%. Interestingly, as in the model by Sébille et al. [11], the model predicts that only by curtailing admission of colonized patients is the eradication of VRE from the ICU possible.

A stochastic simulation analysis of the model was performed by use of 10,000 replications. Each of the 7 events modeled was simulated by use of time-dependent Poisson distributions (with rates corresponding to the current state of the model). The model correctly estimated the numbers of patients admitted during the study period, bed occupancy, and endemic VRE colonization prevalence (36%). Furthermore, the model demonstrated that fluctuations in prevalence of up to ±34%, because of the small numbers involved, were entirely with in 95% confidence bounds. This high degree of variability has important implications for infection control policy; things may get worse even when infection control practices are maintained. Although the long-term behavior predicts an overall reduction in cases due to improvements in hand-washing compliance, etc., chance random events may serve to increase the incidence in the short term. Subsequent work in progress suggests that perhaps one-fifth to one-third of simulated outbreaks may be prolonged after a 50% increase in hand-washing compliance (from 50% to 75%) in some settings.

Independently, Cooper et al. [12] described and analyzed a very similar mathematical model for the spread of handborne nosocomial pathogens, such as S. aureus, in ICUs. As in Austin’s model, stochastic analyses were performed, and they also found that infection control measures such as hand washing could be highly effective in reducing transmission. Although their model was similar in structure, their attention in analyzing the model focused on different questions from that of Austin et al. [9]. Cooper et al. [12] found that the effectiveness of different interventions varied depending on the measure of effectiveness used. For example, improved detection and isolation of colonized patients had little effect on the frequency with which new resistant strains were introduced into the unit but had a substantial effect on reducing the incidence and prevalence of colonization with resistant organisms. Frequency of hand washing had the most dramatic effect in reducing the percentage of patient days during which patients were colonized, compared with a more modest effect on the rate of successful introductions of a resistant strain or the percentage of days on which at least 1 patient was colonized. Their results further demonstrated the importance of chance events in influencing the level of colonization in an ICU, especially in units for which very few individuals enter the unit already colonized with the pathogen of interest [12].

ANTIBIOTIC STRATEGIES

A final model, by Lipsitch et al. [10], described the effects of different antibiotic strategies on the prevalence of antibiotic resistance in hospital. Again, the different patient groups were classified into compartments; patients colonized with sensitive bacteria (“S”), resistant bacteria (“R”) or without colonization of this species (“X”) (figure 3). Patients enter the hospital either colonized with sensitive bacteria (fraction \( m \)) or without this species (fraction \( 1 - m \)). Treatment with antibiotic 1 (at rate \( \tau_1 \), per day) is assumed to eradicate colonization with sensitive bacteria, hence patients from subpopulation \( S \) will, upon receiving treatment, move into subpopulation \( X \). Treatment is not assumed to affect colonization of patients with resistant bacteria (\( R \)). The model also considered treatment with a second drug, antibiotic 2, (at rate \( \tau_2 \), per day), which was assumed to clear carriage of both sensitive and resistant bacteria. Furthermore, the model assumed that both sensitive and resistant bacteria are cleared spontaneously at a rate \( \gamma \) per day. Patients who are not colonized with the bacterial species (\( X \)) are assumed to become colonized at a rate \( \beta S \), equal to the number
of other patients in the hospital who are colonized \((S)\) times a per capita rate constant \(\beta\). Colonization with the resistant strain occurs at a rate \(\beta(1 - c)\), where “\(c\)” denotes the fitness “cost” of resistance to antibiotic 1. The dynamics of the model can once again be expressed by 3 coupled ordinary differential equations.

There are 2 important differences between this model and that described by Austin et al. [9] First, interactions between patients and staff are not captured (i.e., transmission of bacteria is from patient to patient). Second, the model explicitly considers the effect of treatment on the patient’s normal flora, such that a history of treatment (by clearing colonization with sensitive bacteria) places a patient at greater risk of acquiring new colonization.

The model predicted, unsurprisingly, that reducing transmission (captured by the parameter \(\beta\)) via improved infection control would reduce the prevalence of patients colonized with resistant bacteria. Interestingly, however, the model also predicted that reductions of transmission disproportionately reduce the prevalence of resistant bacteria, hardly affecting the prevalence of sensitive bacteria. The latter observation is explained by the fact that carriers colonized with sensitive strains are continuously admitted, whereas resistant bacteria must depend on transmission for colonization success.

A second prediction of the model was that when an intervention to reduce antibiotic use or improve infection control is implemented, the response of bacterial populations is likely to be rapid—weeks to months—because the dynamics of resistance are driven by the replacement of resistant strains by new admissions. Because the mean duration of hospital stay is of the order of 1–2 weeks, it is entirely likely that complete replacement of the patient population is possible within a matter of months.

A further prediction of the model was that increased use of antibiotic 1 will lead to an increase in the prevalence of resistance to this antibiotic. However, increased use of antibiotic 2, for which there is no resistance, will decrease the prevalence of bacteria resistant to antibiotic 1 to complete extinction. Again, the explanation for this lies in the continuous admission of patients colonized with sensitive bacteria. Treatment with antibiotic 2 clears the sensitive strains, thereby increasing the risk of colonization with bacteria resistant to antibiotic 1. However, the treatment also clears colonization in patients harboring resistant strains. The use of antibiotic 2 serves to increase the rate of clearance of resistant and sensitive strains alike, thereby reducing transmission by limiting the average duration (and hence opportunities) that a colonized patient has to spread bacteria. In this sense, taking the hospital as a whole, antibiotic 2 can be thought of as acting analogously to infection control practices. A retrospective analysis of changing antibiotic policies in a single hospital seems to lend support to this hypothesis [14]. The use of gentamicin as the first-choice aminoglycoside was associated with increasing gentamicin resistance among gram-negative bacteria, whereas usage and resistance rates for amikacin were low. A programmed change to amikacin use was associated with a 50% reduction in gentamicin resistance over a period of 26 months. After that period, however, gentamicin was abruptly reintroduced, and this again resulted in a rapid rise in gentamicin resistance. A new change to amikacin again reduced gentamicin resistance, and gentamicin was reintroduced, initially at a modest level and then gradually increased. In doing so, low percentages of gentamicin resistance could be maintained. To the best of our knowledge, such interventions have not been tested prospectively.

**INDIVIDUAL AND POPULATION EFFECTS OF PREVIOUS ANTIBIOTICS**

In an attempt to incorporate patient prescription history, the model is expanded by splitting each of the compartments into 2 subcompartments: those who have not received antibiotic 2 \((S_T, X_T, \text{and } R_T)\) and those who had \((S_U, X_U, \text{and } R_U)\) (figure 4). This permits the use of the model to consider how a history of the use of antibiotic 2 affects an individual patient’s risk of carrying bacteria that are resistant to antibiotic 1. A final, counterintuitive prediction of the model is that the effect of antibiotic 2 on the individual patient’s risk of colonization with bacteria resistant to antibiotic 1 is positive, even though, for the hospital as a whole, as stated above, the increased use of antibiotic 2 is predicted to lower the total prevalence of resistance to antibiotic 1. An intuitive explanation of this surprising result is that treatment with antibiotic 2 not only clears colonization with antibiotic 1-resistant bacteria (thereby reducing carriage of resistant organisms) but also clears carriage of sensitive organisms (thereby making an individual more susceptible to colonization with resistant ones). The balance of these conflicting effects is positive for the unit as a whole but is
that measures to control resistance will take effect more quickly. For example, one of the models described above proposed that individual risk factor analyses will not always correctly predict the magnitude (or even the direction) of change in resistance in response to a particular change in antibiotic policy.

CONCLUSIONS

The models reviewed herein represent some of the first attempts to use mathematical modeling to understand nosocomial cross-transmission and infection-control strategies. The use of mathematical models to study resistance in hospitals is still in its early stages. What use are such models likely to have in the future? One might hope that models of transmission in hospitals could be used, as some other epidemiologic models have been, for relatively detailed forecasting of patterns of resistance and infection in hospitals and ICUs. However, this particular application of models will be difficult in the hospital setting because of the important role played by random variation (stochastic events) in the small populations typically concerned and because of the poorly understood interactions among multiple strains and species colonizing a given individual. Even if models do not prove capable of such precise forecasting, they will have several potential benefits. First, they can provide a theoretical basis for interventions to control infection and resistance, and these interventions can then be subjected to empirical testing. A model may predict, for example, that screening and cohorting of individuals colonized with a resistant organism will have a greater impact than general infection control measures on resistant infections in some settings. These interventions can then be compared in both kinds of settings to test the validity of the model’s prediction. Second, models can suggest explanations for observations that have not been previously explained. For example, one of the models described above proposed that measures to control resistance will take effect more quickly in hospital-acquired than in community-acquired infections because of the influx of patients who carry susceptible bacteria into hospitals. Third, models can help illustrate the range of stochastic variation in incidence and prevalence of colonization with resistant organisms; this may aid in the development of tools that take into account these chance fluctuations when assessing interventions. Finally, by identifying key parameters of the transmission process and predicting approximate rates of change in resistance or other outcome variables following interventions, models can suggest standards for the evaluation of alternative interventions.

APPENDIX

In November 2000, a group of mathematical modelers and clinical investigators met, under the auspices of the European Science Foundation and the European Medical Research Council, in Utrecht, The Netherlands. The aim of the workshop was to discuss the use of mathematical modeling as a tool to investigate preventive strategies for the spread of antibiotic-resistant pathogens within hospitals. The contents of this review represent, to a large extent, the discussions during the workshop. Workshop participants were: R. Anderson (United Kingdom), J. Arends (The Netherlands), D. Austin (United Kingdom), M. Bonten (The Netherlands), M. Bootsma (The Netherlands), C.A.B. Boucher (The Netherlands), C. Brun-Buisson (France), Y. Carmeli (Israel), O. Diekmann (The Netherlands), H. Goossens (Belgium), H. Grundmann (United Kingdom), I.M. Hoepelman (The Netherlands), M. Jones (The Netherlands), J. Kluytmans (The Netherlands), M. Lipsitch (United States), E. Mascini (The Netherlands), H. de Neeling (The Netherlands), J. Rello (Spain), M. Sanchez-Garcia (Spain), P. Terpoorten (The Netherlands), A. Troelstra (The Netherlands), K. Uernl (Germany), C. Vandenburgwe-Grauls (The Netherlands), and J. Verhoef (The Netherlands).

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