tissues can be a source of infection in person-to-person transmission, as reported with corneal transplants [1]. It is feared that exposure to blood and urine may also result in transmission. If this is, in fact, the case, the finding of preferential involvement of highly perfused renal cortex and renal medulla tissues would support the existence of viremia in rabies.

We report that the blood and urine of dogs infected with rabies was not infective at the time of death. Rabies virus RNA was predominantly found in urinary bladder tissue, thus supporting the idea of neural spread of the virus to the urinary bladder.

Four rabies-infected dogs quarantined in the Queen Saovabha Memorial Institute were included in this study. At the time of natural death, samples of urine and blood (obtained by bladder and heart puncture), as well as samples of kidney, ureter, and urinary bladder tissue, and nerve tissue supplying the bladder, were collected. Except for the samples of blood and urine, all samples were stored at −80°C until examination. Two milliliters of urine, 100 µL of whole blood, and 100 mg of each tissue specimen were examined for the presence of rabies virus RNA by nucleic acid sequence–based amplification, as described elsewhere [6]. Urine and blood samples were also subjected to rabies virus isolation in mouse neuroblastoma cells.

Rabies virus could not be isolated from all urine and blood samples. Rabies virus RNA could be recovered from urine samples (obtained from 4 of the 4 dogs), and could also be recovered from bladder (4 of 4), bladder trigone (4 of 4), urethral sphincter (4 of 4), nerve (4 of 4), ureter (3 of 4), renal pelvis (3 of 4), renal medulla (1 of 4), and renal cortex tissues (1 of 4). No rabies virus RNA could be recovered, however, from any of the blood samples obtained from the 4 dogs.

Human-to-human transmission of rabies once a patient with rabies has been admitted to a hospital has always been a serious concern. Other than the report of transmission via corneal transplantation, there are no reliable reports of such transmission [1]. Although rabies virus has been isolated from urine sediment after centrifugation (in 1 of 8 samples) [7], and although the detection of rabies virus RNA in urine samples is as accurate a diagnostic tool as its detection in saliva samples [5], we failed to demonstrate the infectivity of urine. We used uncentrifuged urine to infect neuroblastoma cells. Our findings should therefore be more relevant to the spread of the virus under natural conditions than if we had used centrifuged urine. Failure to detect and isolate rabies virus and its RNA from blood samples supports the previous report that, of 18 patients with rabies, none had virus isolated from their blood samples [7].

Our study suggests that neural spread of the virus to the bladder is the primary event in the progression of infection, with a subsequent propagation of the virus to renal structures. Rabies virus antigen was not found in samples of kidney tissue obtained from 3 human patients with rabies, as described in an earlier report [2]. Although the demonstration of rabies virus antigen or RNA in samples of tissue or biological fluids may help diagnosis [2, 3, 8], it does not necessarily indicate that such a virus is viable.

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isolated, transmission may occur); (2) screening large numbers of patients requires substantial resources, primarily in time, costs of cultures (particularly if the hospital outsources laboratory services), and costs of contact isolation [11]; and (3) contact isolation itself has negative consequences for patients, including reduced contact with health care workers [11]—which may increase the risk of other adverse events [12]—and untoward psychological effects [13]. Many health care epidemiologists are reluctant, in a time of severe cost constraints and critical nurse staffing shortages, to implement an intervention that requires substantial costs up front, increases stress on health care workers, and increases the use of contact isolation. Many have been waiting for data that demonstrate that this approach works not only in an outbreak setting but also as a routine infection-control measure for long-term control of VRE.

Does the study by Calfee et al. [7] demonstrate this? It is not clear from the published results. In their enthusiasm for identifying active surveillance as the key to their control of VRE, they do not adequately recognize several limitations of this noncomparative, observational study. First, although only data from January 1997 through September 1999 (using May 1998 as the “intervention” point) were included in the Poisson regression analysis, the authors in fact started an active surveillance program in 1994—and still saw VRE colonization rates increase during 1997 and 1998. May 1998 represents the intervention point as the “intervention” point) were included in the Poisson regression analysis, the authors in fact started an active surveillance program in 1994—and still saw VRE colonization rates increase during 1997 and 1998. May 1998 represents the time when a third component (computer identification of transfers and printed reminders to units) was added to active surveillance. This third component was followed within 4 months by 2 other interventions: control of antibiotic use and introduction of alcohol-based hand hygiene products. Which intervention was associated with stabilization of the rate of new colonizations? The authors recognize that the other 2 interventions may be confounding variables and subject them to careful scrutiny (we are informed that the antibiotic-control program really did not work very well and that <40% of health care workers were performing hand hygiene procedures when indicated).

Somehow, the intervention of interest (the addition of the third component to active surveillance) escapes this close scrutiny. How many additional patients were screened and identified using this third component? Was compliance with contact isolation observed, as it was with hand hygiene? If so, what was the compliance rate? Identification and isolation of VRE carriers is designed to prevent horizontal transmission; was patient-to-patient transmission confirmed by PFGE? If PFGE was performed, did it show fewer transmission events after the intervention than before? Patients were not isolated until culture results returned; what was the average time to notification of a positive VRE culture? How long, on average, were VRE-positive patients not in isolation, compared with the mean length of stay? If a patient is in the hospital for 4 days, but 3 days are required to determine VRE status, active screening has little impact.

The time period examined in the Poisson regression analysis can also be questioned. The authors report including only the time “when the VRE colonization rate began to increase” [7, p. 238] in the preintervention period and that the postintervention period ended in September 1999. However, post hoc decisions about what time points to examine can easily increase the likelihood of finding a significant difference. Why not include more time points before and after the intervention? Is the difference still significant when the time months from January 1995 through December 1996 (during which time VRE rates were low) are included? And what has happened since 1999? Almost 48 more months of data should now be available, with which the authors could demonstrate a durable impact of their intervention. Those data would be of great interest as well.

None of this is to say that active surveillance does not have a role in VRE control—we use it on high-risk units and for selected high-risk patients in our hospitals. But it will never be uniformly implemented in US health care facilities until a rapid, inexpensive, and sensitive screening test for VRE is widely available and until a well-designed, comparative, multicenter trial demonstrates that it is superior to other potential approaches (e.g., enhanced hand hygiene and risk factor–based isolation strategies). Such a study is being undertaken by the Bacterial and Mycoses Study Group and is now seeking enrollment (D. Goldmann, M. H. Samore, W. C. Huskins, N. O’Grady, and R. Weinstein, personal communication).

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Reply

Sir—In his letter [1], Dr. Diekema asks more questions than we are allowed space to answer, including why most US hospitals have not implemented surveillance culture (SC) programs and contact precautions (CPs) to control nosocomial vancomycin-resistant Enterococcus (VRE) and methicillin-resistant Staphylococcus aureus (MRSA) infections (NVMI). Since 1983, the Centers for Disease Control and Prevention (CDC) has recommended CPs for patients colonized with epidemiologically important antibiotic-resistant pathogens but has not explicitly said that detection of colonized patients was necessary. Many US hospitals do the minimum required for infection control, assuming that this saves money. Northern European countries explicitly recommending SC/CP, however, have controlled endemic MRSA infection to <1% of nosocomial S. aureus infections for years to decades (evidence of sustainability) [2, 3], with very low estimated per capita infection costs [4] and rare adverse effects of (rarely needed) isolation. Diekema [1] also neglected to mention the positive results of all published cost-effectiveness analyses; for example, one analysis found that the costs of SC/CP were 19- to 27-fold lower than those of MRSA bacteremia in a comparable intensive care unit where endemicity was allowed to persist for 51 months (with 75 cases of bacteremia and 14 associated deaths) [5].

Diekema [1] says SCs and CPs are used in his hospital but will not be widely implemented until there is a “well-designed”, randomized, controlled trial (RCT). We disagree with his emphasis on the results of a single study and his self-contradictory implication that there are insufficient data to begin control efforts. Recent meta-analyses of RCTs showed that individual RCTs provide results different from the mean results of all RCTs of the same question as often as did unrandomized epidemiologic studies of that same question [6, 7], which suggests that Hill [8] was right to emphasize the need for consistent results from multiple studies by different investigators in different populations before it is concluded that an association is causal. Consistent NVMI control with SC/CP has been reported in numerous studies [9], as have high strength of association, reversibility, and specificity, several more of Hill’s causal criteria [8]. We encourage interested readers to read the Society for Healthcare Epidemiology of America (SHEA) guideline on this topic [9], accessible at http://www.shea-online.org/PositionPapers.html.

RCTs examining the usefulness of active surveillance for VRE and MRSA likely have not been conducted because (1) they are expensive, (2) neither the National Institutes of Health nor the CDC wished to support RCTs of controlling NVMI during the last 3 decades of the 20th century, (3) many unrandomized studies have shown control of NVMI with SC/CP, and (4) some consider it unethical to randomize patients to suboptimal protection against potentially lethal infection [10]. The occurrence of intra- and interhospital spread means that the optimal unit of randomization should not be individual patients, wards, or even hospitals. A recent study showed spread of 2 MRSA strains to all 12 study hospitals throughout 7 states, accounting for three-fourths of MRSA infections in the study hospitals [11]. Without randomization of large clusters (i.e., each cluster large enough to render spread from contiguous nonparticipating wards/hospitals negligible), transmission from surrounding areas will bias such an RCT toward the null hypothesis. The proposed RCT mentioned by Diekema [1], however, randomizes an individual ward or two inside otherwise nonparticipating hospitals where NVMI spread is known to be frequent and where compliance with experimental SC/CP may be suboptimal. It also proposes comparison of SC/CP with hand hygiene more aggressive than most hospitals have been able to consistently achieve, potentially limiting durability and reproducibility.

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