Impacts of Age at Kasai Operation on Its Results in Late Childhood and Adolescence: A Rational Basis for Biliary Atresia Screening
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Impact of Age at Kasai Operation on Its Results in Late Childhood and Adolescence: A Rational Basis for Biliary Atresia Screening

Marie-Odile Serinet, MD, Barbara E. Wildhaber, MD, PhD, Pierre Broué, MD, Alain Lachaux, MD, Jacques Sarles, MD, Emmanuel Jacquemin, MD, PhD, Frédéric Gauthier, MD, Christophe Chardot, MD, PhD

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The authors have indicated they have no financial relationships relevant to this article to disclose.

What’s Known on This Subject
Increased age at the time of Kasai operation for BA has a negative effect on its short-term results in infancy and early childhood.

What This Study Adds
Increased age at surgery has a continuous and sustained deleterious effect on the results of the Kasai operation until adolescence. Our data represent a rational basis for BA screening to reduce the need for LTs in infancy and childhood.

ABSTRACT
BACKGROUND. Increased age at surgery has a negative impact on results of the Kasai operation for biliary atresia in infancy and early childhood. It remained unclear if an age threshold exists and if this effect persists with extended follow-up. In this study we examined the relationship between increased age at surgery and its results in adolescence.

METHODS. All patients with biliary atresia who were living in France and born between 1986 and 2002 were included. Median follow-up in survivors was 7 years.

RESULTS. Included in the study were 743 patients with biliary atresia, 695 of whom underwent a Kasai operation; 2-, 5-, 10-, and 15-year survival rates with native liver were 57.1%, 37.9%, 32.4%, and 28.5%, respectively. Median age at Kasai operation was 60 days and was stable over the study period. Whatever the follow-up (2, 5, 10, or 15 years), survival rates with native liver decreased when age at surgery increased (≤30, 31–45, 46–60, 61–75, and 76–90 days). Accordingly, we estimated that if every patient with biliary atresia underwent the Kasai operation before 46 days of age, 5.7% of all liver transplantations performed annually in France in patients younger than 16 years could be spared.

CONCLUSIONS. Increased age at surgery had a progressive and sustained deleterious effect on the results of the Kasai operation until adolescence. These findings indicate a rational basis for biliary atresia screening to reduce the need for liver transplantations in infancy and childhood.

BILIARY ATRESIA (BA) is a perinatal disease of unclear etiology, characterized by inflammation and obliteration of intrahepatic and extrahepatic bile ducts, leading to cholestasis and cirrhosis. The currently recommended treatment is sequential: in the first weeks of life, the Kasai operation aims to bypass the obstructed extrahepatic bile ducts and to restore the biliary flow. When this procedure fails to clear jaundice and/or complications associated with biliary cirrhosis appear, secondary liver transplantation (LT) is needed. Altogether, ~20% of the patients can reach the age of 20 years with their native liver, and 10% can reach the age of 30 years.

Several prognostic factors of the Kasai operation have been related to the short-term results of this procedure. Among them are many that can not be altered, such as anatomy of the biliary remnant, histology of the liver, portal pressure at the time of Kasai operation, or association of BA with polysplenia (BA splenic malformation syndrome). Other prognostic factors of BA are related to the organization of care to these patients, and therefore are improvable: age at Kasai operation, accessibility to LT, experience of the center in the management of patients with BA. Although some discordant results have been published regarding the impact of age at surgery (Table 1), large series concordantly show that short-term results of the Kasai operation are better when surgery is performed early in life. Whether an age threshold exists remains unclear, with published series often being divided at 45 or 60 days for statistical purposes. Furthermore, the follow-up of the series is often limited, and whether the age effect persists in later childhood and adolescence is uncertain. Therefore, the possible benefits of a neonatal screening policy are difficult to evaluate.

On the basis of the analysis of the series of all patients with BA born in France between 1986 and 2002, this study
examined: (1) the impact of age at Kasai operation on survival with native liver (SNL) in later childhood and adolescence; and (2) the expected benefits if the Kasai operation was performed earlier in every patient because of a BA screening.

PATIENTS AND METHODS

The charts of all children with BA or suspected BA treated in France since LT became available were reviewed by the investigators of the study, who visited the participating centers and analyzed the charts locally. All 45 pediatric centers (including medical, surgical, and LT units) involved in the management of patients with BA in France contributed to this survey; therefore, data collection was exhaustive.

Inclusion criteria and registered data have been described extensively for the French national outcome study.\(^1\) In summary, all patients with BA who were living in France and born between 1986 and 2002 were included. The diagnosis of BA was critically reassessed by the investigators of the study by consultation of the charts of every patient before inclusion in the study. Results of histologic examination of the biliary remnants were available in 584 (78%) patients. The median follow-up in survivors was 7 years (range: 0.2–18.1 years).

### Ethical Approval

This study received the agreement of French authorities (Commission Nationale de l’Informatique et des Libertés, authorization 997085). The registry was strictly confidential. Each family received an information letter indicating the aims and methods of the study and had the possibility to check or correct the data recorded for their child.

### Statistical Analysis

Survival rates were estimated according to the Kaplan Meier method. SNL ends at LT or at death (in patients

### TABLE 1 Variations of Outcome According to Age at Kasai Operation in Reported Series

<table>
<thead>
<tr>
<th>Age Threshold, Effect</th>
<th>Follow-up and End Points</th>
<th>No. of Patients</th>
<th>Origin of Study</th>
<th>Year</th>
<th>Study</th>
</tr>
</thead>
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<tr>
<td>&lt;30 d, unfavorable</td>
<td>Age at LT</td>
<td>92</td>
<td>St Louis Children’s Hospital (US)</td>
<td>2001</td>
<td>17</td>
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<tr>
<td>&lt;30 d, favorable</td>
<td>4-y SNL</td>
<td>349</td>
<td>Multicenter study (Canada)</td>
<td>2007</td>
<td>16</td>
</tr>
<tr>
<td>&lt;46 d, favorable</td>
<td>10-y SNL and 10-y OS</td>
<td>164</td>
<td>University Hospital Kremlin-Bicêtre, Paris (France)</td>
<td>1997</td>
<td>32</td>
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<td></td>
<td>5- and 10-y SNL</td>
<td>472</td>
<td>Multicenter study (France)</td>
<td>1999</td>
<td>6</td>
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<tr>
<td></td>
<td>5-y and 10-y OS</td>
<td>252</td>
<td>Multicenter study (France)</td>
<td>2006</td>
<td>11</td>
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<tr>
<td>&lt;8 wk, favorable</td>
<td>Clearance of jaundice</td>
<td>159</td>
<td>Chulalongkorn University, Bangkok (Thailand)</td>
<td>2005</td>
<td>33</td>
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<tr>
<td></td>
<td>Clearance of jaundice</td>
<td>50</td>
<td>King’s College, London (United Kingdom)</td>
<td>1989</td>
<td>34</td>
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<tr>
<td>&lt;60 d, favorable</td>
<td>5-y and 10-y SNL</td>
<td>141</td>
<td>National Taiwan University Hospital, Taipei (Taiwan)</td>
<td>2006</td>
<td>35</td>
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<td>5-y OS (=SNL)</td>
<td>904</td>
<td>Multicenter study (US)</td>
<td>1990</td>
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<td>Actuarial OS</td>
<td>21</td>
<td>University of Oslo (Norway)</td>
<td>1993</td>
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<td>Clearance of jaundice</td>
<td>62</td>
<td>Prince of Songkla University, Songkhla (Thailand)</td>
<td>2003</td>
<td>37</td>
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<tr>
<td></td>
<td>Clearance of jaundice</td>
<td>200</td>
<td>Tohoku University Hospital, Sendai (Japan)</td>
<td>1983</td>
<td>38</td>
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<td></td>
<td>Bile flow</td>
<td>41</td>
<td>Childrens Hospital of Los Angeles (US)</td>
<td>1989</td>
<td>39</td>
</tr>
<tr>
<td>&lt;2 mo, favorable</td>
<td>3-y OS (=SNL)</td>
<td>21</td>
<td>University of Colorado, Denver (US)</td>
<td>1980</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>10-y SNL</td>
<td>122</td>
<td>University Hospital Kremlin-Bicêtre, Paris (France)</td>
<td>1990</td>
<td>41</td>
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<tr>
<td>&lt;7 wk, favorable</td>
<td>2-y SNL</td>
<td>36</td>
<td>University Hospital Munich (Germany)</td>
<td>2000</td>
<td>42</td>
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<tr>
<td>&lt;10 wk, favorable</td>
<td>SNL</td>
<td>266</td>
<td>University of Colorado, Denver (US)</td>
<td>1993</td>
<td>43</td>
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<tr>
<td>&lt;10.5 wk, favorable</td>
<td>4-y SNL</td>
<td></td>
<td>University of Colorado, Denver (US)</td>
<td>1979</td>
<td>44</td>
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<tr>
<td>&lt;12 wk, favorable</td>
<td>Clearance of jaundice</td>
<td>93</td>
<td>University of Hong Kong (Hong Kong)</td>
<td>1997</td>
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<tr>
<td>&lt;90 d, favorable</td>
<td>20-y SNL</td>
<td>63</td>
<td>University Hospital Kremlin-Bicêtre, Paris (France)</td>
<td>2005</td>
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<td></td>
<td>Clearance of jaundice</td>
<td>66</td>
<td>Indiana University School of Medicine, Indianapolis (US)</td>
<td>1989</td>
<td>46</td>
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<tr>
<td>Related (no defined threshold, younger age at surgery was observed in groups with successful Kasai operation)</td>
<td>5-y SNL</td>
<td>1381</td>
<td>Multicenter study (Japan)</td>
<td>2003</td>
<td>47</td>
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<tr>
<td>No significant effect of age at Kasai operation</td>
<td>Clearance of jaundice</td>
<td>108</td>
<td>University of Tubingen (Germany)</td>
<td>1998</td>
<td>9</td>
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<td></td>
<td>Actual SNL</td>
<td>47</td>
<td>Hospital of Porto Alegre (Brazil)</td>
<td>2002</td>
<td>48</td>
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<tr>
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<td>Actual SNL</td>
<td>49</td>
<td>Booth Hall Children’s Hospital, Blackley, Manchester (United Kingdom)</td>
<td>2000</td>
<td>49</td>
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<tr>
<td></td>
<td>Clearance of jaundice</td>
<td>29</td>
<td>University of Alberta (Canada)</td>
<td>1996</td>
<td>50</td>
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<td></td>
<td>1-y SNL</td>
<td>75</td>
<td>Chulalongkorn University, Bangkok (Thailand)</td>
<td>2006</td>
<td>51</td>
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<td>2-y SNL</td>
<td>104</td>
<td>Multicenter study (US)</td>
<td>2007</td>
<td>12</td>
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<td></td>
<td>5-y SNL</td>
<td>93</td>
<td>Multicenter study (United Kingdom)</td>
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<td>52</td>
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<td>5-y SNL</td>
<td>338</td>
<td>King’s College, London (United Kingdom)</td>
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<td></td>
<td>5-y OS (=SNL)</td>
<td>117</td>
<td>Juntendo University (Tokyo)</td>
<td>1993</td>
<td>56</td>
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<tr>
<td></td>
<td>3-y SNL</td>
<td>27</td>
<td>Ege University, Izmir (Turkey)</td>
<td>2004</td>
<td>57</td>
</tr>
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<td></td>
<td>OS (=SNL)</td>
<td>34</td>
<td>University of Michigan, Ann Arbor (US)</td>
<td>1991</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Clearance of jaundice</td>
<td>31</td>
<td>University of Michigan, Ann Arbor (US)</td>
<td>2002</td>
<td>59</td>
</tr>
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<td></td>
<td>Clearance of jaundice</td>
<td>31</td>
<td>Emory University, Atlanta (US)</td>
<td>2001</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Clearance of jaundice</td>
<td>35</td>
<td>Juntendo University, Tokyo (Japan)</td>
<td>1985</td>
<td>61</td>
</tr>
</tbody>
</table>

OS indicates overall survival.
RESULTS

A total of 743 children were included. The detailed medical history of the patients has been reported in the French national outcome study. Briefly, a total of 695 (93.5%) children with BA underwent the Kasai operation or a derived procedure, 48 (6.5%) children with BA did not undergo the Kasai operation. Median age at Kasai operation was 60 days (range: 12–180 days). No significant variation of the age at Kasai operation was observed during the 17 years of the study (Fig 1). SNL after the Kasai operation was 57.1% at 2 years of age (SE: 1.9%; 363 patients alive with native liver), 37.9% at 5 years of age (SE: 2.0%; 177 patients alive with native liver), 32.4% at 10 years of age (SE: 2.0%; 86 patients alive with native liver), and 28.5% at 15 years of age (SE: 2.3%; 22 patients alive with native liver).

SNL decreased when age at Kasai operation increased \( (P < .001) \) (Fig 2). The best results were obtained if the Kasai operation was performed before the age of 30 days, and then decreased regularly with increased age at operation. Nevertheless, patients operated after the age of 90 days still had a 13% chance of surviving with their native liver until adolescence. The effect of age at Kasai operation lasted in late childhood and adolescence (Fig 2).

As described in the French national outcome study, increased age at Kasai operation was independently, from other prognostic factors (such as polysplenia syndrome or unfavorable anatomic patterns of the extrahepatic biliary remnant), associated with a worse SNL outcome.

The comparison between patients who underwent the Kasai operation before the age of 46 days versus patients who underwent the Kasai operation later and patients without contraindications to surgery who did not undergo the Kasai operation (the main reason being delayed diagnosis in most of them), showed a 12.1% difference of 15-year SNL between the 2 groups (Fig 3). Consequently, the estimation of the possible benefits of early Kasai operation (performed before 46 days of life in all patients with BA) was calculated according to the following data: A = number of new BA cases per year; 743/17 years = 43.7/year; B = 15-year SNL for patients operated before 46 days of life: 34.9%; C = 15-year SNL for patients operated after 45 days of life or patients without contraindications to surgery who did not undergo the Kasai operation: 22.8%; D = ratio of patients with BA operated after 45 days of life or patients without contraindications to surgery who did not undergo the Kasai operation: 72.6%; E = number of liver grafts per patient who had received a transplant: 456 grafts in 386 patients who received a transplant = 1.18 graft per patient who received a transplant.

The estimated savings of liver grafts in infancy and childhood, if every patient with BA underwent the Kasai

![FIGURE 1](image-url)
operation before 46 days of life, are 4.5 liver grafts per year \[= A \times D \times (B-C) \times E\], which represents 5.7% of all pediatric LTs performed annually in France (2000–2005: 476 pediatric LTs = 79 LTs per year. Source: Agence de la Biomédecine, Paris, France).

**DISCUSSION**

Although numerous reports have shown that late performance of the Kasai operation worsens its results (Table 1), the real impact of age at the time of Kasai operation has remained controversial.\(^{15}\) To establish the potential benefits of mass screening for BA, 2 main issues remained unclear: (1) does the prognosis of the Kasai operation progressively decrease when age at surgery increases, and what happens to children operated in the first month of life? and (2) Does the better short-term prognosis observed after early Kasai operations persist or fade in late childhood and adolescence?

In the present large series, we found that the earlier the Kasai operation, the better its results. Especially in the subgroup of 59 patients operated on in the first month of life, the outcome was better than in the children operated on later in life. These findings correlate with data from the Canadian national study, in which 21 patients with BA operated on before the age of 1 month...
had a better SNL than 291 patients operated on when older. These results contrast with a previous study focusing on the results of the Kasai operation performed in the first month of life, the outcome seemed worse in the 9 of 92 patients who underwent the Kasai operation in the first month of life, suggesting that early diagnosis might have been related to a different pathogenesis of the disease, associated with a worse prognosis. Noteworthy, in the detailed analysis of prognostic factors of Kasai operation in the French series, classical factors of poor prognosis such as polysplenia syndrome, or unfavorable anatomy of the extrahepatic biliary remnant, were found to be independent of age at surgery by multivariate analysis.

Whether the benefit of an early Kasai operation would last in late childhood and adolescence remained uncertain. It has been shown that most of the patients with BA alive with their native livers at the ages of 10 years and 20 years had undergone the Kasai operation with BA alive with their native livers at the ages of 10 years and 20 years. It has been shown that most of the patients would last in late childhood and adolescence remained uncertain. It has been shown that most of the patients would last in late childhood and adolescence, remained uncertain. It has been shown that most of the patients would last in late childhood and adolescence.16 Our data confirm these findings in a larger series, and show that whatever the follow-up in childhood, survival rate with native liver increased when age at surgery decreased (Fig 2). To evaluate the potential benefits of a realistic mass screening, we compared the children operated before 46 days to the rest of the patients without contraindications to surgery. The threshold of 45 days was chosen, because in many countries the first visit with the pediatrician is at the end of the first month of life, and in case of suspected cholestasis, the diagnosis of BA seems realistic in the next 2 weeks. This comparison showed a 12.1% difference of 15-year SNL (34.9% vs 22.8%) between the 2 groups. From our data, a rough estimation showed that if the Kasai operation was performed before 46 days in every patient, 4.5 pediatric LTs could be spared each year, representing 5.7% of all pediatric LTs performed annually in France.

What would be the impact of such a pediatric LT-saving policy? Reducing the need for scarce pediatric liver grafts would shorten the transplantation waiting list and reduce the need for living related donors, whose risks cannot be neglected (the morbidity rate of left lobectomy is estimated at 10%). The very long-term adverse effects of prolonged immunosuppression are still incompletely known, but impaired renal function (that may lead to chronic renal failure), dyslipidemia, diabetes, and increased risk of malignancy are certain. Delaying transplantation after infancy and avoiding Epstein-Barr virus primary infection in an immunosuppressed child might reduce the risk of posttransplant lymphoproliferative disease. Today, the results of LT in adults are close to those in pediatric patients, especially with diseases that do not recur after LT, such as BA.

Reducing pediatric LTs would also lead to significant financial savings. In France, the estimated first-year cost for LT is 100 000 Euros, and the estimated annual follow-up charges are 20 000 Euros. The costs of follow-up of a patient with BA who has not received a transplant are not well known but are undoubtedly less than those of a transplanted child. In a scenario where the annual charges of a patient with BA who has not received a transplant would be 10 000 Euros, the total savings for the 4.5 yearly economized pediatric LTs in France would amount to ~500 000 Euros per year. In the United States, the same savings of 5.7% of all pediatric LTs would represent 32.7 LTs per year (4016 pediatric LTs were performed in the United States between 2000 and 2006 [ie, 574 pediatric LTs per year (www.unos.org)]). The estimated first-year charge for a LT is ~450 000 dollars, and the estimated annual follow-up charges are ~30 000 dollars. In a scenario where the charges of a patient with BA who has not received a transplant would be 15 000 dollars, the total financial savings would amount to ~18 million dollars per year. Therefore, BA screening programs seem to be a cost-effective investment for society.

Despite repeated attempts to sensitize medical staff to check the color of stools in the first month of life, the age at Kasai operation did not decrease in France during the 17 years of the study, with a stable median age at Kasai operation of 60 days. Recently, a special mention has been added in the French individual health booklet of each infant, to inform the parents to check the color of the stools of their infants, and another information campaign to parents and health professionals is currently underway. It is too early to evaluate the benefits of these actions. In other countries, several screening methods have been proposed. Currently, the most simple and effective method seems to be the stool color card, introduced by Matsui and Kodori in Japan, and also used in Argentina and Taiwan. Systematic checking of stool color before the end of the first month of life is a sensitive method to detect cholestasis. The costs of such a screening program are limited, and are most likely inferior to the savings obtained by the spared LTs; this was evaluated in Switzerland by a financial simulation within a project for the executive MBA in management of technology at the Swiss Federal Institute of Technology, Lausanne and the University of Lausanne, Switzerland (M. Minder, MBA Launch plan for BA screening card, unpublished data, November 2007). A national pilot study of such BA screening is under way in Switzerland.

At the other end of the spectrum, our data also show that late Kasai operations (performed after the age of 3 months) still can help avoid some LTs in infancy and childhood: 15-year SNL was 13.4% in this subgroup of patients. Therefore, as already emphasized by other studies, the Kasai operation should not be systematically denied after 3 months. Nevertheless, a precise preoperative checkup is necessary to detect patients with advanced liver disease (presenting with signs such as ascites, impaired synthetic functions, reversed portal flow and/or arterial diastolic flow) and orient them to primary LT.

**CONCLUSIONS**

Increased age at surgery had a progressive and sustained deleterious effect on the results of the Kasai operation.
REFERENCES


25. Jacquemin E. Screening for biliary atresia and stool colour:


OUR PIGS, OUR FOOD, OUR HEALTH

“The late Tom Anderson, the family doctor in this little farm town in northwestern Indiana, at first was puzzled, then frightened. MRSA (methicillin-resistant Staphylococcus aureus) sometimes arouses terrifying headlines as a ‘superbug’ or ‘flesh-eating bacteria.’ The best-known strain is found in hospitals, where it has been seen regularly since the 1990s, but more recently different strains also have been passed among high school and college athletes. The federal Centers for Disease Control and Prevention reported that by 2005, MRSA was killing more than 18 000 Americans a year, more than AIDS. Dr Anderson at first couldn’t figure out why he was seeing patient after patient with MRSA in a small Indiana town. And then he began to wonder about all the hog farms outside of town. Could the pigs be incubating and spreading the disease? One of the first clues that pigs could infect people with MRSA came in the Netherlands in 2004, when a young woman tested positive for a new strain of MRSA, called ST398. The family lived on a farm, so public health authorities swept in—and found that 3 family members, 3 co-workers and 8 of 10 pigs tested all carried MRSA. Since then, that strain of MRSA has spread rapidly through the Netherlands—especially in swine-producing areas. A small Dutch study found pig farmers there were 760 times more likely than the general population to carry MRSA (without necessarily showing symptoms), and Scientific American reports that this strain of MRSA has turned up in 12% of Dutch retail pork samples. Now this same strain of MRSA has also been found in the United States. A new study by Tara Smith, a University of Iowa epidemiologist, found that 45% of pig farmers she sampled carried MRSA, as did 49% of the hogs tested. The study was small, and much more investigation is necessary.”

Noted by JFL, MD
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