Epidemic Profile of Shiga-Toxin–Producing Escherichia coli O104:H4 Outbreak in Germany

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ABSTRACT

BACKGROUND
We describe an outbreak of gastroenteritis and the hemolytic–uremic syndrome caused by Shiga-toxin–producing Escherichia coli in Germany in May, June, and July, 2011. The consumption of sprouts was identified as the most likely vehicle of infection.

METHODS
We analyzed data from reports in Germany of Shiga-toxin–producing E. coli gastroenteritis and the hemolytic–uremic syndrome and clinical information on patients presenting to Hamburg University Medical Center (HUMC). An outbreak case was defined as a reported case of the hemolytic–uremic syndrome or of gastroenteritis in a patient infected by Shiga-toxin–producing E. coli, serogroup O104 or serogroup unknown, with an onset of disease during the period from May 1 through July 4, 2011, in Germany.

RESULTS
A total of 3816 cases (including 54 deaths) were reported in Germany, 845 of which (22%) involved the hemolytic–uremic syndrome. The outbreak was centered in northern Germany and peaked around May 21 to 22. Most of the patients in whom the hemolytic–uremic syndrome developed were adults (88%; median age, 42 years), and women were overrepresented (68%). The estimated median incubation period was 8 days, with a median of 5 days from the onset of diarrhea to the development of the hemolytic–uremic syndrome. Among 59 patients prospectively followed at HUMC, the hemolytic–uremic syndrome developed in 12 (20%), with no significant differences according to sex or reported initial symptoms and signs. The outbreak strain was typed as an enteroaggregative Shiga-toxin–producing E. coli O104:H4, producing extended-spectrum beta-lactamase.

CONCLUSIONS
In this outbreak, caused by an unusual E. coli strain, cases of the hemolytic–uremic syndrome occurred predominantly in adults, with a preponderance of cases occurring in women. The hemolytic–uremic syndrome developed in more than 20% of the identified cases.
On May 19, 2011, the Robert Koch Institute, Germany’s national-level public health authority, was informed about a cluster of three cases of the hemolytic–uremic syndrome in children admitted on the same day to the university hospital in the city of Hamburg. On May 20, a team from the Robert Koch Institute arrived in Hamburg to assist with the public health investigation. It quickly became clear that the case numbers were continuing to rise, that there were also cases in adults, and that other areas of Germany, especially northern Germany, were also affected. An investigation of the outbreak involving all levels of public-health and food-safety authorities was initiated to identify the causative agent and the vehicle of infection in order to prevent further cases of disease. Sprouts were eventually identified as the most likely vehicle of infection.

The hemolytic–uremic syndrome, which was first described in children in the 1950s, is characterized by the triad of acute renal failure, hemolytic anemia, and thrombocytopenia. Diarrhea-associated hemolytic–uremic syndrome occurs predominantly in children, and a precipitating infection with Shiga-toxin–producing *Escherichia coli*, mainly of serotype O157:H7, is the primary cause. The usual reservoir for these bacteria is ruminants, particularly cattle. Human infection with Shiga-toxin–producing *E. coli* occurs through the inadvertent ingestion of fecal matter — for example, through contaminated food or water or through contact with animals or their farm environment or, secondarily, through contact with infected humans. In contrast, in adults, the hemolytic–uremic syndrome with prodromal diarrhea, indicating an infectious cause, is a rare event. For example, from 1989 through 2006, only 21 of the 322 adults (7%) listed in the Oklahoma registry as having thrombotic thrombocytopenic purpura or the hemolytic–uremic syndrome presented with bloody diarrhea.

Earlier, we presented descriptive epidemiologic, clinical, and microbiologic information on the unusual outbreak in Germany in a preliminary report (available at NEJM.org). This report updates and finalizes this information.

**METHODS**

**GERMAN SURVEILLANCE SYSTEM**

According to the German Protection against Infection Act of 2001, the detection of a Shiga toxin (Stx) in *E. coli* isolates or of its encoding gene (stx) in stool enrichment culture or isolates must, by law, be reported by diagnosing laboratories to local health departments. This reporting process allows the identification of Shiga-toxin–producing *E. coli* infection independently of serogroup (serotyping information is requested but not required). The German case definition of Shiga-toxin–producing *E. coli* gastroenteritis (without the hemolytic–uremic syndrome) requires, besides laboratory confirmation, the presence of at least one of the following symptoms: diarrhea (three or more loose stools in a 24-hour period), abdominal cramps, or vomiting.

In addition, physicians are required to report clinical symptoms compatible with diarrhea-associated hemolytic–uremic syndrome in a patient. The German case definition of the hemolytic–uremic syndrome comprises thrombocytopenia (platelet count of <150,000 per cubic millimeter), hemolytic anemia, and acute renal dysfunction. The third criterion is met if at least one of the following findings is present: an increase in the serum creatinine level (unspecified), oliguria, anuria, proteinuria, or hematuria.

Reported cases of the hemolytic–uremic syndrome or Shiga-toxin–producing *E. coli* infection were investigated and recorded by the local health department, and the reports were forwarded electronically, without identifying information, through the state to the federal level. Disease onset was defined as the onset of diarrhea, regardless of whether the hemolytic–uremic syndrome developed at a later date. An outbreak case was defined as a reported case of the hemolytic–uremic syndrome or a reported case of gastroenteritis in a patient infected by Shiga-toxin–producing *E. coli*, of serogroup O104 or unknown serogroup, with a disease onset during the period from May 1 through July 4, 2011, in Germany. We describe here data from the national reporting database on infectious diseases as of September 19, 2011. The descriptive analysis focuses primarily on reported cases of the hemolytic–uremic syndrome as indicators for the entire outbreak. To show the outbreak area, a map of the incidence of the disease according to county was generated (Fig. 1). Cases were attributed to a particular county if that county was the probable place of infection.

**CLINICAL INFORMATION**

We analyzed clinical data from two groups of pa-
Figure 1. Incidence of the Hemolytic–Uremic Syndrome According to County in Germany.
The incidence shown is per 100,000 population. A total of 845 cases were detected in this outbreak. Cases are attributed to a particular county if that county was the probable site of infection.
patients at the Hamburg University Medical Center (HUMC): patients who were positive for stx at their first presentation to the HUMC during the period from May 19 through June 1 (a cross-sectional analysis of data extracted from electronic medical records) and a prospectively assembled hospital-based cohort of adults who were seen from May 25 through June 6 at a special unit that was set up during the outbreak. The study protocol for the cohort study was approved by the ethics committee of the Hamburg Chamber of Physicians. Patients were enrolled in the study if they presented with bloody diarrhea or if they had any diarrhea after contact with a patient who had Shiga-toxin–producing E. coli infection. All patients provided written informed consent. Patients were followed for at least 14 days and were tested for the outbreak strain according to the protocol of the National Consulting Laboratory on Hemolytic–Uremic Syndrome. Only data from patients infected by the outbreak strain were included in the analysis. The proportion of patients with the hemolytic–uremic syndrome among all patients who were positive for Shiga-toxin–producing E. coli was calculated. Platelet counts and creatinine and lactate dehydrogenase levels were monitored daily.

To estimate the proportion of nonbloody diarrhea, bloody diarrhea (without the hemolytic–uremic syndrome), and the hemolytic–uremic syndrome among patients who were thought to be infected with E. coli O104, we pooled the data from six cohorts that were investigated by public health authorities during the course of the outbreak — originally with the intention of identifying the most likely vehicle of infection. We describe the frequencies and proportions of self-reported (bloody) diarrhea and clinically diagnosed hemolytic–uremic syndrome irrespective of the results of microbiologic diagnosis.

MICROBIOLOGIC ANALYSIS

Shiga-toxin–producing E. coli infection was diagnosed by private microbiologic laboratories either by screening for Stx with the use of one of several commercially available enzyme immunoassays or by detection of stx with the use of polymerase chain reaction (PCR). The National Reference Center for Salmonella and Other Bacterial Enteric Pathogens confirmed the presence of Shiga-toxin–producing E. coli, cultured the isolates, and characterized the Shiga-toxin–producing E. coli in samples from local or regional laboratories that were positive for Stx or stx. Chromogenic agar media for Enterobacteriaceae that were positive for extended-spectrum beta-lactamase (ESBL) were used for isolation of the strain. Biochemical characterization of the strain was performed with the use of various commercially available tests (VITEK, bioMérieux; MicroPlate GN, BIOLOG; and API, bioMérieux). Shiga-toxin–producing E. coli virulence-factor genes (stx1, stx2, eae, and ehx) were detected by established PCR methods. The presence of virulence-factor genes that are typical of enterohaemorrhagic E. coli, such as aatA, aggR, aap, aggA and aggC, were detected according to established PCR protocols. Antimicrobial susceptibility was tested by means of microdilution assays with the use of minimal inhibitory concentrations according to the guidelines of the European Committee on Antimicrobial Susceptibility Testing. Serotyping of Shiga-toxin–producing E. coli followed standard protocols. One-enzyme (XbaI) pulsed-field gel electrophoresis was performed on Shiga-toxin–producing E. coli O104:H4 isolates. Given the strain’s properties, a shortened protocol was recommended by the National Consulting Laboratory on Hemolytic–Uremic Syndrome and was used by the National Reference Center and HUMC for confirmation of the outbreak strain.

STATISTICAL ANALYSIS

For statistical comparisons, the z test was used for proportions, and the Mann–Whitney U test for age distribution. The incubation period was estimated on the basis of data from selected patients with the hemolytic–uremic syndrome or Shiga-toxin–producing E. coli gastroenteritis for whom the date of onset of diarrhea was known. They either had stayed in northern Germany for no more than 48 hours or were part of disease clusters with known date and place of exposure. The interval between the date of onset of diarrhea and the date of diagnosis of the hemolytic–uremic syndrome was calculated with the use of information from the clinician’s notification form, which was sent without identifying information to the Robert Koch Institute.
RESULTS

OUTBREAK CASES
A total of 3816 cases reported to public health authorities in Germany with onset dates during the period from May 1 through July 4, 2011, were attributed to the outbreak: 845 cases of the hemolytic–uremic syndrome, including 36 fatal cases (4.2%; 95% confidence interval [CI], 3.0 to 5.8), and 2971 additional cases of Shiga-toxin–producing E. coli gastroenteritis (all laboratory-confirmed), including 18 fatal cases (0.6%; 95% CI, 0.4 to 1.0). Thus, the hemolytic–uremic syndrome developed in 22% of the patients ascertained in this outbreak. The number of cases of hemolytic-uremic syndrome during the outbreak period was almost 70 times the number that had occurred during this period in previous years.

The outbreak grew dramatically starting on May 8; cases of the hemolytic–uremic syndrome peaked on May 21, and cases of Shiga-toxin–producing E. coli gastroenteritis peaked on May 22 (Fig. 2), with a median date of hospitalization for the hemolytic–uremic syndrome of May 24. Among patients who died, death occurred a median of 10 days after the onset of the disease. The first patients who had laboratory-confirmed infection with the outbreak strain became ill on May 8 (for earlier outbreak cases, information on serogroup was not available).

Cases of the hemolytic–uremic syndrome were reported from all 16 states in Germany. The highest incidences were reported from the northern states of Hamburg (10.0 cases per 100,000 population), Schleswig–Holstein (6.9 cases per 100,000), Bremen (2.7 cases per 100,000), Meck-
The incidence of the disease around the city of Hamburg was centered in the northern Germany outbreak area, where the area with high incidences (2.5 to 30 reported cases per 100,000 population) was centered. Satellite clusters linked to restaurants in eastern North Rhine-Westphalia and southern Hesse, the area with high incidences (2.5 to 30 reported cases per 100,000 population) was centered around the city of Hamburg.

A total of 88% of the case patients with the hemolytic–uremic syndrome in this outbreak were adults (i.e., persons older than 17 years of age). Among case patients 17 years of age or younger, the median age was 11 years. Only 2% of the case patients with the hemolytic–uremic syndrome were younger than 5 years of age, as compared with 69% of case patients with the hemolytic–uremic syndrome reported in Germany from 2001 through 2010.11 The median age of all patients with the hemolytic–uremic syndrome in the outbreak was 42 years. The median age of case patients with the hemolytic–uremic syndrome who died was 74 years (range, 20 to 91, except for one 2-year-old boy), and the median age of patients with Shiga-toxin–producing E. coli gastroenteritis who died was 82 years (range, 38 to 89). Among women, the incidence of the hemolytic–uremic syndrome peaked in the age group of 25 to 29 years (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

A total of 68% of the case patients with the hemolytic–uremic syndrome and 58% of the case patients with Shiga-toxin–producing E. coli gastroenteritis were female; among the patients in the two groups who died, 75% and 50%, respectively, were female. The proportion of male case patients with the hemolytic–uremic syndrome rose from 30% among the patients with a disease onset in May to 46% among the patients with disease onset in June (P=0.02).

On the basis of data from 91 case patients, we estimated that the median incubation period for this pathogen in this outbreak was 8 days (interquartile range, 6 to 10), without an apparent difference between cases of Shiga-toxin–producing E. coli gastroenteritis and cases of the hemolytic–uremic syndrome. Among 98 case patients for whom data on both the date of onset of diarrhea and the date of onset of the hemolytic–uremic syndrome were known, the interval from the onset of diarrhea to the diagnosis of the hemolytic–uremic syndrome was 5 days (interquartile range, 4 to 7).

**CLINICAL INFORMATION**

Data on 166 patients, obtained at their first presentation to HUMC, were analyzed; 143 of the patients (86%) were adults; 62% were female. No patient had a fever (defined as a temperature of at least 38.5°C) at the first presentation. Bloody diarrhea was reported less often in children than in adults (64% [14 of 22 children] vs. 91% [126 of 138 adults], P<0.001), whereas abdominal pain was a very common symptom in both children and adults, occurring in 93% of the children (13 of 14) and in 88% of the adults (121 of 137). Vomiting occurred more often in children than in adults (72% [13 of 18 children] vs. 18% [20 of 114 adults], P<0.001). Most patients did not have significantly elevated leukocyte levels (most were within the normal range; in some cases, counts were approximately 13,000 per cubic millimeter) or C-reactive protein levels (typically about 15 to 35 mg per liter [normal level, <5 mg per liter]). A total of 40 patients (24%) already met the criteria for the hemolytic–uremic syndrome at the time of presentation. Clinical and laboratory values in adults and children, stratified according to the presence or absence of the hemolytic–uremic syndrome, are summarized in Table 1.

Among the 135 patients who were followed in the hospital-based cohort, the outbreak strain was detected in 59 (44%), and the hemolytic–uremic syndrome developed in 12 of these patients (20%; 95% CI, 11 to 33). Demographic and clinical characteristics at presentation did not differ significantly between patients with diarrhea in whom the hemolytic–uremic syndrome developed and those in whom it did not develop (Table 2). An examination of the platelet counts and creatinine and lactate dehydrogenase levels 5 days before through 2 days after the onset of the syndrome in 22 patients with the hemolytic–uremic syndrome (Fig. 3) indicates that the development of the hemolytic–uremic syndrome was sudden.

In six closed cohorts, 127 of 416 persons reported having had diarrhea, of whom 27 (21%) were clinically diagnosed with the hemolytic–
Shiga-Toxin–Producing E. coli Outbreak in Germany

Microbiologic Features
The serotype of the E. coli outbreak strain is O104:H4. The strain ferments sorbitol within 24 hours and is positive for lactose and beta-glucuronidase. The pathogen possesses genes typical of enteroaggregative E. coli, such as attA, aggR, aap, aggA, and aggC, located on a virulence plasmid. In addition, the strain carries the gene for a Shiga-toxin 2 variant (stx2a). Other typical Shiga-toxin–producing E. coli genes such as stx1, eae, and ehx are missing. All isolates classified as the outbreak strain are resistant to beta-lactam antibiotics (e.g., ampicillin) and third-generation cephalosporins and are partially resistant to fluoroquinolones (nalidixic acid). The strain is sensitive to carbapenems and ciprofloxacin. The outbreak strain produces an ESBL complex (CTX-M15) and beta-lactamase TEM-1. The National Reference Center typed 1023 isolates of this outbreak clone. A total of 120 of these were analyzed by pulsed-field gel electrophoresis; all had indistinguishable patterns.

Discussion
We describe the epidemiologic characteristics of an outbreak of infection with Shiga-toxin–producing E. coli O104:H4. There were more than 800 incident cases of the hemolytic–uremic syndrome in this outbreak during the period from May 1 through July 4, 2011, and altogether more than 3800 cases of disease. In addition, as many as 15 other countries, including the United States, reported cases occurring among people who had traveled to northern Germany: 51 cases of the hemolytic–uremic syndrome (including 2 deaths) and 89 cases of Shiga-toxin–producing E. coli gastroenteritis. The outbreak probably began on May 8; however, because not every case was laboratory-confirmed and serotyped, we cannot be sure that there were not earlier cases.
Table 2. Demographic and Clinical Characteristics of Patients Positive for Shiga-Toxin–Producing Escherichia coli (STEC) Who Were Followed Prospectively.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=59)</th>
<th>Without HUS (N=47)</th>
<th>With HUS (N=12)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>38.6±14.0</td>
<td>38.5±13.3</td>
<td>38.9±16.8</td>
<td>0.93</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>23 (39)</td>
<td>18 (38)</td>
<td>5 (42)</td>
<td>0.76</td>
</tr>
<tr>
<td>Reported fever — no./total no. (%)</td>
<td>4/55 (7)</td>
<td>4/46 (9)</td>
<td>0/9 (0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Bloody diarrhea — no./total no. (%)</td>
<td>48/58 (83)</td>
<td>37/46 (80)</td>
<td>10/12 (83)</td>
<td>0.87</td>
</tr>
<tr>
<td>Interval between onset of diarrhea and first presentation in STEC unit — days</td>
<td>4.1±4.7</td>
<td>4.0±5.0</td>
<td>4.1±3.3</td>
<td>0.98</td>
</tr>
<tr>
<td>Stool frequency — no. of stools/day</td>
<td>9.4±8.9</td>
<td>9.9±9.6</td>
<td>7.4±5.4</td>
<td>0.47</td>
</tr>
<tr>
<td>Abdominal pain — no. (%)</td>
<td>46 (78)</td>
<td>35 (74)</td>
<td>11 (92)</td>
<td>0.24</td>
</tr>
<tr>
<td>Vomiting — no. (%)</td>
<td>11 (19)</td>
<td>7 (15)</td>
<td>4 (33)</td>
<td>0.15</td>
</tr>
<tr>
<td>Previous contact with other patients with STEC — no. (%)</td>
<td>13 (22)</td>
<td>11 (23)</td>
<td>2 (17)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Data are for patients who were prospectively followed at the STEC unit of the Hamburg University Medical Center between May 25 and June 6, 2011.
† P values are for the presence versus the absence of the hemolytic–uremic syndrome.

There are important differences between this outbreak and previous outbreaks of Shiga-toxin–producing E. coli infection,13–18 such as the one that occurred in Japan in 1996, in which there were 121 cases of the hemolytic–uremic syndrome — all in children.14 First, the hemolytic–uremic syndrome represents more than 20% of the ascertained cases, which is a much larger percentage than in other outbreaks. Second, the majority of the cases of the hemolytic–uremic syndrome (88%) occurred in adults rather than in children, with the majority occurring in women. Third, the causative agent was a Shiga-toxin–producing E. coli strain of serotype O104:H4.

The outbreak strain combines the virulence properties of two different diarrhea-causing E. coli pathotypes: typical enteroaggregative E. coli and Shiga-toxin–producing E. coli. The outbreak strain carries the chromosomal backbone of a typical enteroaggregative E. coli strain.19,20 It is likely that it has acquired the bacteriophage encoding stx2 and other genetic elements.20–22 Similar but not identical enteroaggregative Shiga-toxin–producing E. coli — even of serotype O104:H4 — have been isolated previously, albeit rarely, from patients with the hemolytic–uremic syndrome23,24 (e.g., in 2001 from two siblings in Germany in whom the hemolytic–uremic syndrome had developed25). Since typical enteroaggregative E. coli are isolated primarily from humans,26 the origin of this outbreak may not have been zoonotic.

Two observations suggest that the pathogen in this outbreak is exceptionally virulent. First, the hemolytic–uremic syndrome developed in a large proportion of patients — 22% of case patients ascertained in the German surveillance system for infectious diseases, 20% of prospectively observed patients with Shiga-toxin–producing E. coli diarrhea at a hospital in Hamburg, and 21% of persons in closed cohorts investigated during the course of the outbreak. These proportions are consistently higher than those in previous outbreaks13–18 and higher than the proportion (6%) ascertained through active surveillance of Shiga-toxin–producing E. coli O157:H7, the virulent prototype of Shiga-toxin–producing E. coli, in the United States.27 Second, the outbreak strain caused the hemolytic–uremic syndrome in 101 children even though the strain lacked the intestinal adherence factor intimin (encoded by the gene eae); eae-negative strains have previously been isolated from adults with the hemolytic–uremic syndrome28 but rarely from children. For example, 97% of Shiga-toxin–producing E. coli isolated from children with the hemolytic–uremic syndrome in Germany and Austria carried the eae gene.29 Another unique feature of this outbreak, probably attributable to the pathogen, was the estimated median incubation period of 8 days, which was longer than the 3-day to 4-day incubation period reported for Shiga-toxin–producing E. coli O157:H7.13,30

The patients affected in this outbreak were mainly adults, and even among pediatric case patients with the hemolytic–uremic syndrome, the median age was considerably higher than...
that of pediatric case patients in other years; the median age of 11 years in the outbreak surveillance data was supported by a median age of 11.8 years among 33 outbreak case patients at HUMC’s pediatric nephrology unit. It is unclear whether this atypical age distribution of cases primarily reflects patterns of sprout consumption or is attributable to the specific properties of this outbreak strain — or both. Furthermore, it remains to be elucidated why women were overrepresented among the cases of the hemolytic–uremic syndrome. The predominance of women among the case patients may be driven by the food vehicle if women are more health conscious and thus more likely to eat sprouts. Toward the end of the outbreak, when secondary household transmission probably contributed a larger proportion of cases, there was a shift to a more even sex distribution. No sex difference was observed with respect to the risk of development of the hemolytic–uremic syndrome among a limited sample of patients with diarrhea who were prospectively followed in the hospital-based cohort.

The most common clinical sign in adults was bloody diarrhea accompanied by abdominal cramps. The clinical presentation in adults differed from that in children. Bloody diarrhea occurred significantly more often in adults — irrespective of the presence or absence of the hemolytic–uremic syndrome — whereas vomiting was reported more frequently in children. Clinical symptoms such as abdominal pain, bloody diarrhea, and the frequency of loose stools did not differ between patients in whom the hemolytic–uremic syndrome developed and those in whom it did not. Changes in laboratory values, indicating renal failure and hemolysis, occurred quickly, often within 24 hours (Fig. 3). Daily laboratory testing of platelet counts and creatinine and lactate dehydrogenase levels appeared to be pivotal for the early diagnosis of the hemolytic–uremic syndrome, and these laboratory tests were more sensitive than were patient-reported symptoms and the physical examination. Indeed, several patients reported that they had begun to recover from bloody diarrhea several days after the initial presentation, at the same time as the onset of the hemolytic–uremic syndrome. For many reported cases, information on exact symptoms (e.g., diarrhea or bloody diarrhea) and additional microbiologic information were not available. Consequently, although the clinical picture of the hemolytic–uremic syndrome in adults appeared to be very specific for this outbreak, among the cases of Shiga-toxin–producing E. coli diarrhea, those unrelated to this outbreak could not be efficiently filtered out owing to the lack of serotype information in many reported cases.

In summary, this outbreak exemplifies the threat posed by foodborne pathogens with their propensity to cause large common-source outbreaks. These outbreaks may have unusual disease patterns and sometimes affect new population subgroups.
Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the physicians and laboratory personnel, who were working under intense strain and yet kept up their notification requirements; local and state health departments for quickly passing on case data to the Robert Koch Institute; and epidemiologists in other countries for providing detailed travel and disease information regarding patients with travel-associated cases.

REFERENCES


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SHIGA-TOXIN–PRODUCING E. COLI OUTBREAK IN GERMANY

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