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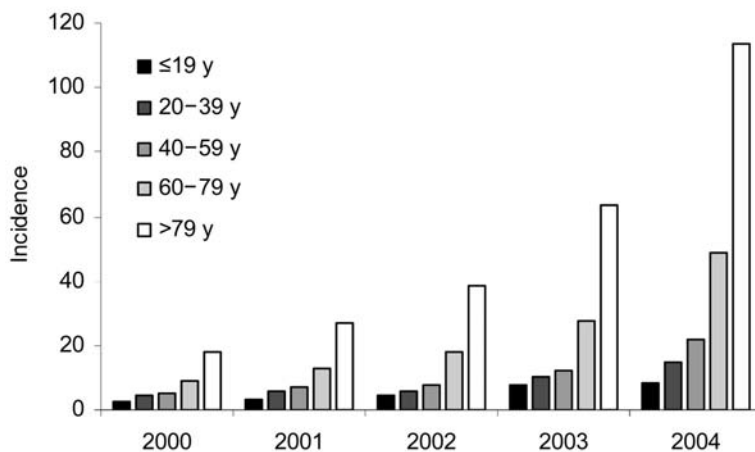


Figure. Incidence of *Clostridium difficile*-associated disease per 100,000 inpatients upon discharge from hospitals in Germany.

sis of discharge data to compare findings from the United States with data from Germany. We therefore determined the absolute number of inpatient discharges from all hospitals in Germany with the number of discharge diagnoses of CDAD reported in the national Statistische Bundesamt for the years 2000–2004. We then calculated the incidence of CDAD as a discharge diagnosis for each year and stratified our results by age groups (Figure).

Our results confirm the observations from the United States. The effect of *C. difficile* on illness of patients in hospitals in Germany has escalated dramatically. This is true especially for patients ≥ 60 years of age. This trend indicates the need for increased awareness of this pathogen and a concerted effort to control CDAD by reducing unnecessary antimicrobial drug use and implementing currently recommended infection control measures. It also highlights the need to develop more rapid and accurate diagnostic tools and more effective prevention and treatment strategies.

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Human Bocavirus in Febrile Children, the Netherlands

To the Editor: Human bocavirus (HBoV) is a recently discovered virus of the family *Parvoviridae*, genus *Bocavirus*, which appears to cause widespread respiratory tract infections (RTI) in children. In selected groups of children with RTI, detection rates have varied from 2.8% to 11.3% (1–9). However, the exact prevalence and pathogenic effects of this virus remain to be established.

During a prospective cohort study to evaluate the prognosis of fever at a general practice after-hours service in Rotterdam, nasopharyngeal swabs were collected from febrile children and tested for respiratory viruses, including HBoV. We report the incidence and clinical features of HBoV infection in these children.

From June 1, 2005, through January 16, 2006, all children 3 months to 6 years of age whose parents contacted the after-hours service because of fever, as reported by parents and not further defined, were eligible for inclusion in the study. Children were excluded when the parents could not communicate in Dutch ($n = 77$) and if the child had already been included within the past 2 weeks ($n = 11$). A research nurse visited the child at home within 24 hours of inclusion. The child was physically examined, and a nasopharyngeal swab and a blood sample for C-reactive protein measurement were collected. The parents subsequently recorded the child's symptoms in a diary for 7 days. The Central Committee on Research Involving Human Subjects, the Netherlands, approved this study.

Nucleic acids were isolated on a MagnaPure isolation station (Roche Applied Science, Penzberg, Germany) and subsequently analyzed by real-time assays. Detection of HBoV was performed by using a primers set and a

fluorescein amidite-labeled TaqMan probe directed against sequences of the NP1 gene. (Sequences are available from the corresponding author.) Testing was routinely done for the following viruses: influenza virus types A and B, parainfluenza virus types 1–4, respiratory syncytial virus (RSV) types A and B, adenovirus, coronavirus (OC43, 229E, and NL63), and rhinovirus.

Nasopharyngeal swabs were collected from 257 (81%) of 319 enrolled children. The overall virus detection rate was 52.9%; most frequently detected were adenovirus (11%), RSV-A (10.5%), parainfluenza virus type 1 (8.5%), and rhinovirus (8%). Five children were included twice; none of them was HBoV positive. The PCR for HBoV was positive in 4 children (1.6%), all boys. The characteristics of these children are shown in the Table.

All 4 children reported rhinorrhea and cough. Patient 1 reported abdominal pain, diarrhea (more than twice daily, with mucus), dyspnea, and a skin rash, along with respiratory symptoms. All symptoms lasted for >1 week. At physical examination, the research nurse evaluated the children to be not ill or (slightly) ill, based on standard criteria. Patient 1 had a skin rash and palpable cervical lymph nodes. Patient 4 had palpable lymph nodes and red tonsils.

Patient 1 was given amoxicillin for otitis media, and patient 4 received amoxicillin for tonsillitis, as diagnosed by the general practitioner on

the basis of the patient's clinical symptoms, without bacteriologic confirmation. During a 1-week follow-up period, none of the patients sought further medical advice.

Our finding that HBoV may cause RTI is in accordance with the literature (1–6). Our findings support those of others in suggesting a role for HBoV in systemic infection, causing gastrointestinal symptoms and skin rash (6,8).

Our detection rate, in general practice, is lower than the rates reported from former studies of children with RTI (3%–10%) (1–8). Coinfection of HBoV and other viruses was found among 3 (75%) of 4 children (Table). In other studies, coinfection was found in 17.6%–55.6% (mainly adenovirus, RSV, and human metapneumovirus) (1,2,5,7–9). The other detected viruses could have caused the symptoms of patients 2–4. However, HBoV was the only detected virus in 1 child with respiratory symptoms, gastrointestinal symptoms, and rash, and therefore might be the pathogen. Considering the high amount of HBoV in patient 3, symptoms were likely caused by HBoV in this patient as well.

Our ability to analyze severity of disease in our study population was limited because all children had mild disease, and no child was hospitalized. However, all children reported a prolonged course of fever, >7 days or recurrent within 1 week. This finding is in contrast with the mean duration of fever of 2.6 days in the study of

Arnold et al., which was based in a hospital setting (6). In our study, none of the HBoV-positive children received a diagnosis of bronchiolitis, pneumonia, or bronchitis, as in previous studies. None of the 4 children in our study was born preterm, compared with 19%–44% of HBoV-positive children in previous studies (5,6). None had a positive history for asthma or other underlying diseases, as did up to 50% of the children in previous studies (1,6).

In conclusion, HBoV was detected in nasopharyngeal swabs of 4 (1.6%) of 257 children <6 years of age whose parents contacted a general practice after-hours service. Our results suggest that HBoV might cause mild disease with respiratory and gastrointestinal symptoms and skin rash. Further research, not restricted to susceptible or hospitalized patients, is needed to clarify the prevalence and pathogenicity of this new virus in the general population.

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Table. Characteristics of children with human bocavirus infection, the Netherlands*

Patient no.	Age, y	Month detected	Symptoms	Body temperature (°C)	CRP (mg/L)	Positive PCR (log copies/mL)
1	2.3	Nov 2005	Earache, rhinorrhea, cough, sore throat, abdominal pain, diarrhea, skin rash, dyspnea, increased breathing rate	36.2	9	Bocavirus (4.20)
2	1.9	Nov 2005	Rhinorrhea, cough, sore throat, vomiting, increased breathing rate	38.8	26	Rhinovirus (7.57), RSV B (5.51), bocavirus (2.88)
3	1.3	Dec 2005	Earache, rhinorrhea, cough, headache, vomiting, skin rash, increased breathing rate	38.6	26	Bocavirus (6.72), parainfluenza virus 4 (4.11), adenovirus (2.00)
4	1.0	Jan 2006	Earache, rhinorrhea, cough, sore throat, abdominal pain, diarrhea, vomiting	37.7	88	Adenovirus (6.90), bocavirus (2.88)

*CRP, C-reactive protein; RSV, respiratory syncytial virus.

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Dengue Virus Serotype 3, Karachi, Pakistan

To the Editor: The global prevalence of dengue fever (DF) has grown dramatically in recent decades; DF is now endemic to >100 countries (*1*). Dengue hemorrhagic fever (DHF), a potentially lethal complication of dengue virus infection, was first recognized in Asia in the 1950s and is now a leading cause of hospitalization and death among children (*1*). During the past decade, DHF epidemics have occurred in China, Sri Lanka, India, the Maldives, Bangladesh, and Pakistan (*2–4*).

In Pakistan, an outbreak of DHF was first reported in Karachi in 1994 (*4*). Through mid-2005, 15–20 patients with DF or DHF were admitted each year to the Aga Khan University Hospital (AKUH), a tertiary care referral center in Karachi. Many more cases, however, may have gone unrecognized. Ours is the first report of dengue virus serotype 3 in Pakistan.

From September through December 2005, at least 3 major hospitals in Karachi, including AKUH, had a sudden increase in the number of patients with signs consistent with the World Health Organization definition of DHF: high fever, rash, epistaxis, gum bleeding, liver dysfunction, and thrombocytopenia (platelets <100,000/mm³); most had evidence of capillary leakage in the form of raised hematocrit and pleural effusion with or without ascites (*5*). Because in Pakistan, Crimean-Congo hemorrhagic fever (CCHF) is an important differential diagnosis for hemorrhagic fever, most patients seen at AKUH received care in strict isolation and were empirically treated with ribavirin. At time of admission, blood samples were collected for serologic testing for dengue virus and reverse transcription (RT)–PCR testing for

CCHF virus. The first 5 samples, collected during the initial 2 weeks of the outbreak, were also sent to the Special Pathogens Reference Unit, Centre for Emergency Preparedness and Response, Health Protection Agency, Salisbury, United Kingdom, for diagnostic confirmation. In the absence of a local surveillance and disease notification system, the number of patients with suspected DHF at different hospitals in Karachi could not be ascertained.

Of the 106 patients who had a clinical diagnosis compatible with DHF (*5*), 9 (8.5%) died and 97 (91.5%) recovered. Patients with possible DF (fever, mild thrombocytopenia with platelets >100,000/mm³) were not admitted and were treated as outpatients. Dengue virus infection was confirmed for 42 of the 106 patients. Serum samples from 39 patients contained anti-dengue virus immunoglobulin M (IgM) antibody (Chemicon, Temecula, CA, USA). Diagnosis for 6 of these patients was confirmed by using immunoblot tests (Dengue IgM Blot and Dengue IgG Blot, Genelabs Diagnostics, Singapore). Of the 9 patients who died, 6 had dengue IgM and IgG according to immunoblot testing, and 3 had dengue IgM according to ELISA. Diagnoses for 3 additional patients were confirmed by RT-PCR.

An RT-PCR assay specific for dengue viruses (*6*) was used to amplify the C/PrM/M region of the genome and produced PCR products of the expected size in 3 patient samples: 2 (K1 and 2) from Karachi and 1 (B) from Balochistan. The PCR products were sequenced, and data were subsequently placed in GenBank under accession numbers DQ469827 for D3418-05 (patient K1), DQ469828 for D3419-05 (patient K2), and DQ469826 for D3417-05 (patient B). These data were compared with those in databases by using the basic local alignment search tool for nucleotides (blastn), with default settings (*7*). For