EHEC O104 outbreak 2011 in Germany: What have we learned

Tim Eckmanns

on behalf of the Dept for Infectious Disease Epidemiology,

Robert Koch Institute,

Berlin, Germany

Paris, October 21, 2011

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Course of the first days (I)

- Thursday May 19:
  - Phone call from the local health department in Hamburg
  - Official invitation from local authority in Hamburg
- Friday May 20:
  - RKI forwards information to the Federal Centre for Risk Assessment (BfR) and the Ministry of Health (BMG)
  - First team is sent to Hamburg
  - first interviews with patients
- Saturday May 21:
  - First qualitative hints towards vegetables communicated to food safety authorities
  - First case-control study is initiated

Source: RKI. Sachstandsbericht EHEC/HUS O104:H4 Ausbruch, 7.9.2011

Course of the first days (II)

- Sunday May 22:
  - Analysis of first case-control study
  - First information sent to the European Early Warning and Response System (EWRS) and WHO
  - dpa-Interview: hints about raw vegetables
- Monday May 23:
  - Information made available on the Internet
  - Preparation for the second case-control study
- Tuesday May 24:
  - First notification within international Health Regulations
  - Second case-control study is initiated

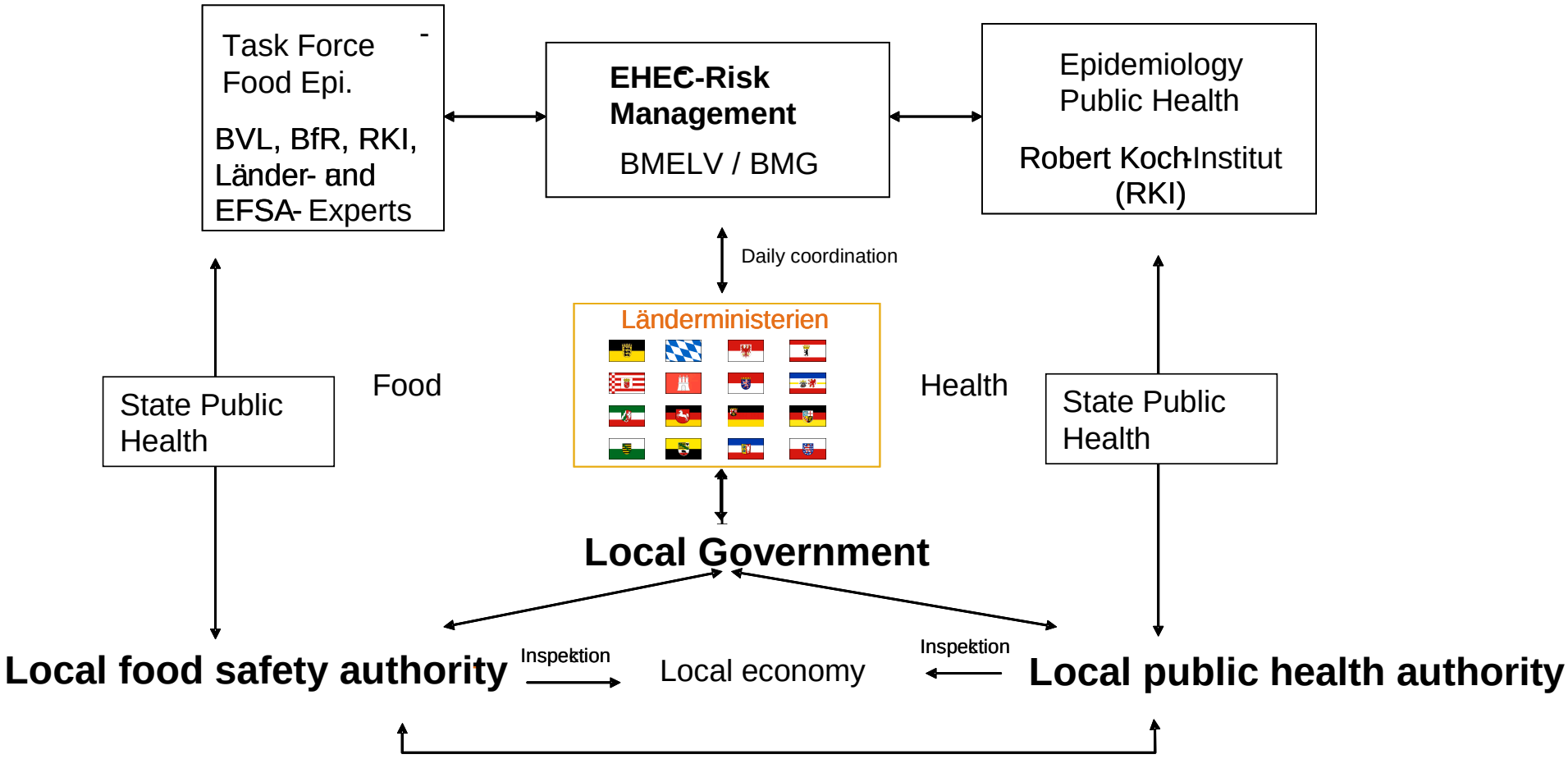
Source: RKI. Sachstandsbericht EHEC/HUS O104:H4 Ausbruch, 7.9.2011

Course of the first days (III)

- Wednesday May 25:
  - Identification of pathogen by the RKI and consiliar laboratory (STEC O104:H4, Shiatoxin2, ESBL)
  - Press conference with BfR + RKI: results of the second case-control study, recommendation about food consumption
- Thursday May 26:
  - Information in English made available on the Internet
  - Scientific publication
    - Epidemiologisches Bulletin
    - Eurosurveillance

Quelle: RKI. Sachstandsbericht EHEC/HUS O104:H4 Ausbruch, 7.9.2011

Inter-agency cooperation to identify vehicles and source of the infection



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STEC / HUS surveillance

- **Routine Surveillance**
  - Passive: STEC infection and „enteropathic“ HUS are staturorily notifiable to local health departments in Germany, and transmitted via states to the RKI
  - Active: Surveillance of pediatric HUS in cooperation with German Society of pediatric nephrology (monthly inquiries)
- **Outbreak surveillance**
  - Active Surveillance (daily/weekly) of bloody diarrhea in emergency departments
  - Sentinel surveillance (convenience sample) with laboratories to timely assess the trend in STEC incidence during the outbreak
  - Daily query on treatment capacities in nephrologic clinics

Basic description of the outbreak

(as of 16 August 2011)

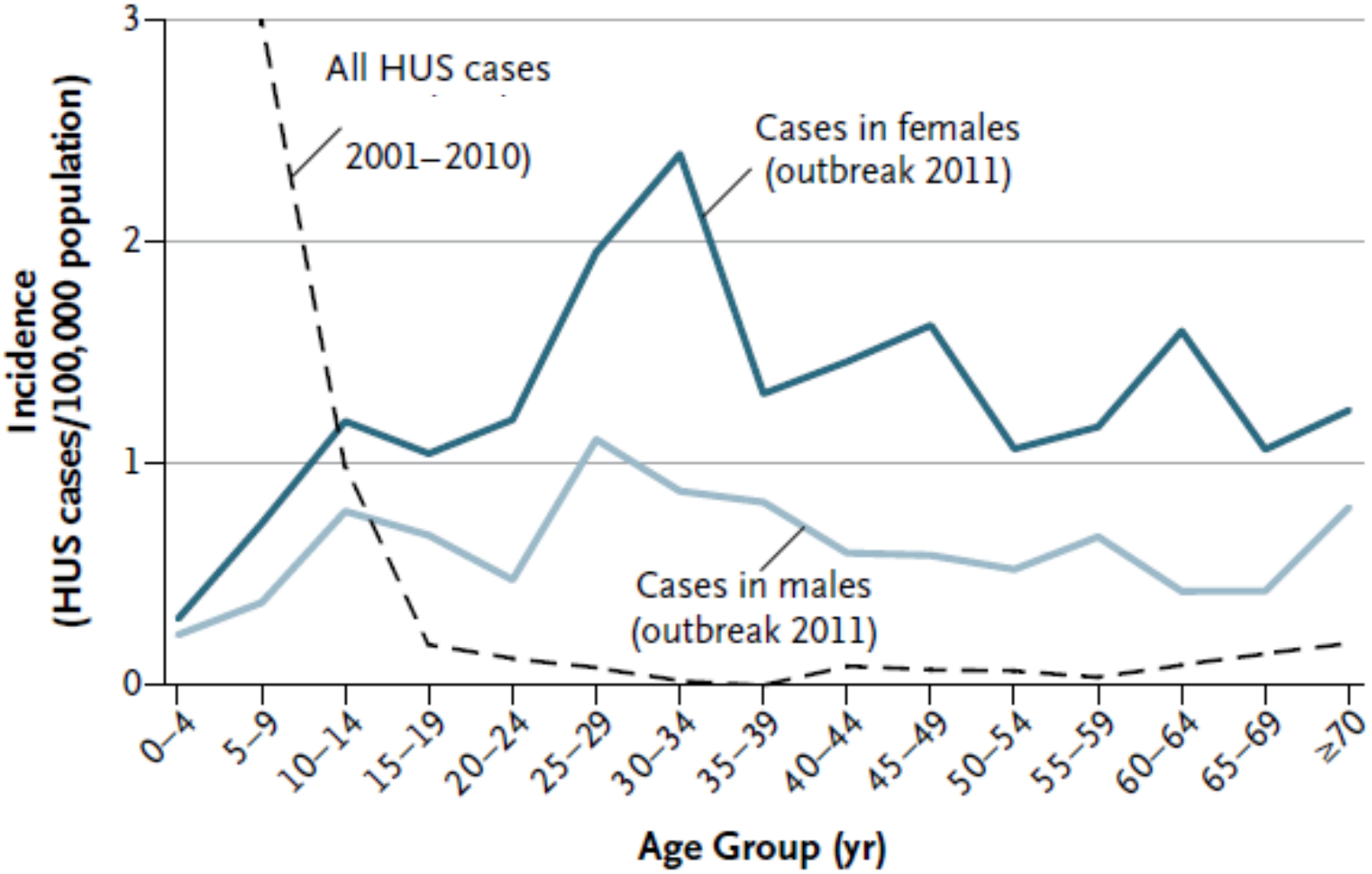
	STEC*	HUS**
N, (%)	2987 (78)	855 (22)
Median age [yr]	46	42
Female [%]	58	68
Deaths	18	37
Case-fatality ratio [%]	0.6	4.1
Hospitalisation [%]	54	100

* STEC O104 or, if serogroup unknown, Stx / *stx* positive but not Stx1/ *stx1* – *only* from 1 May through 4 July

** suspected and confirmed

Reported HUS incidence by age and sex

(Status as of June 17, 2011)



Source: Frank C, Werber D, Cramer JP et al. NEJM 2011

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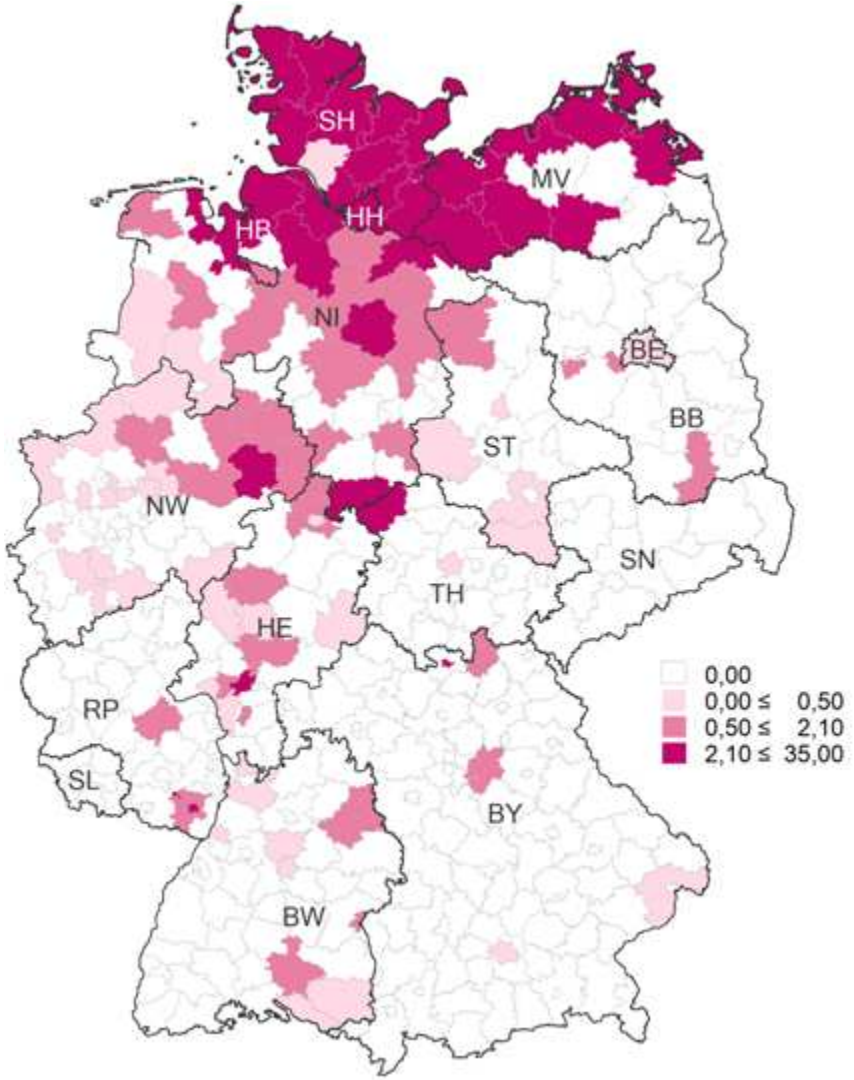
HUS incidence (Cases/100,000 inhabitants) by suspected place of infection (Status as of 3. Sept. 2011)



Source: RKI. Sachstandsbericht EHEC/HUS O104:H4 Ausbruch, 7.9.2011

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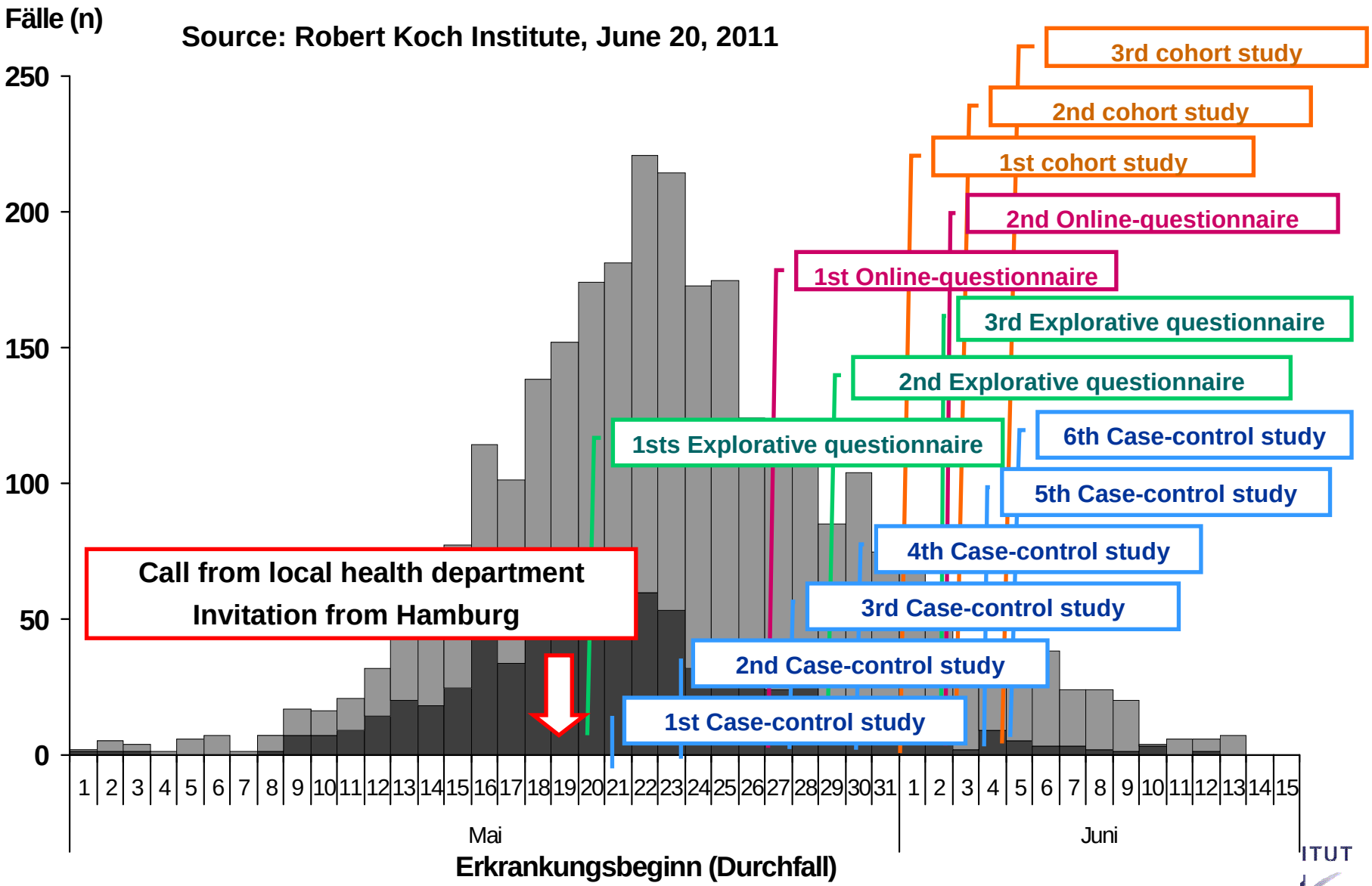
Timeline of epidemiological studies



Source: RKI. Sachstandsbericht EHEC/HUS O104:H4 Ausbruch, 7.9.2011

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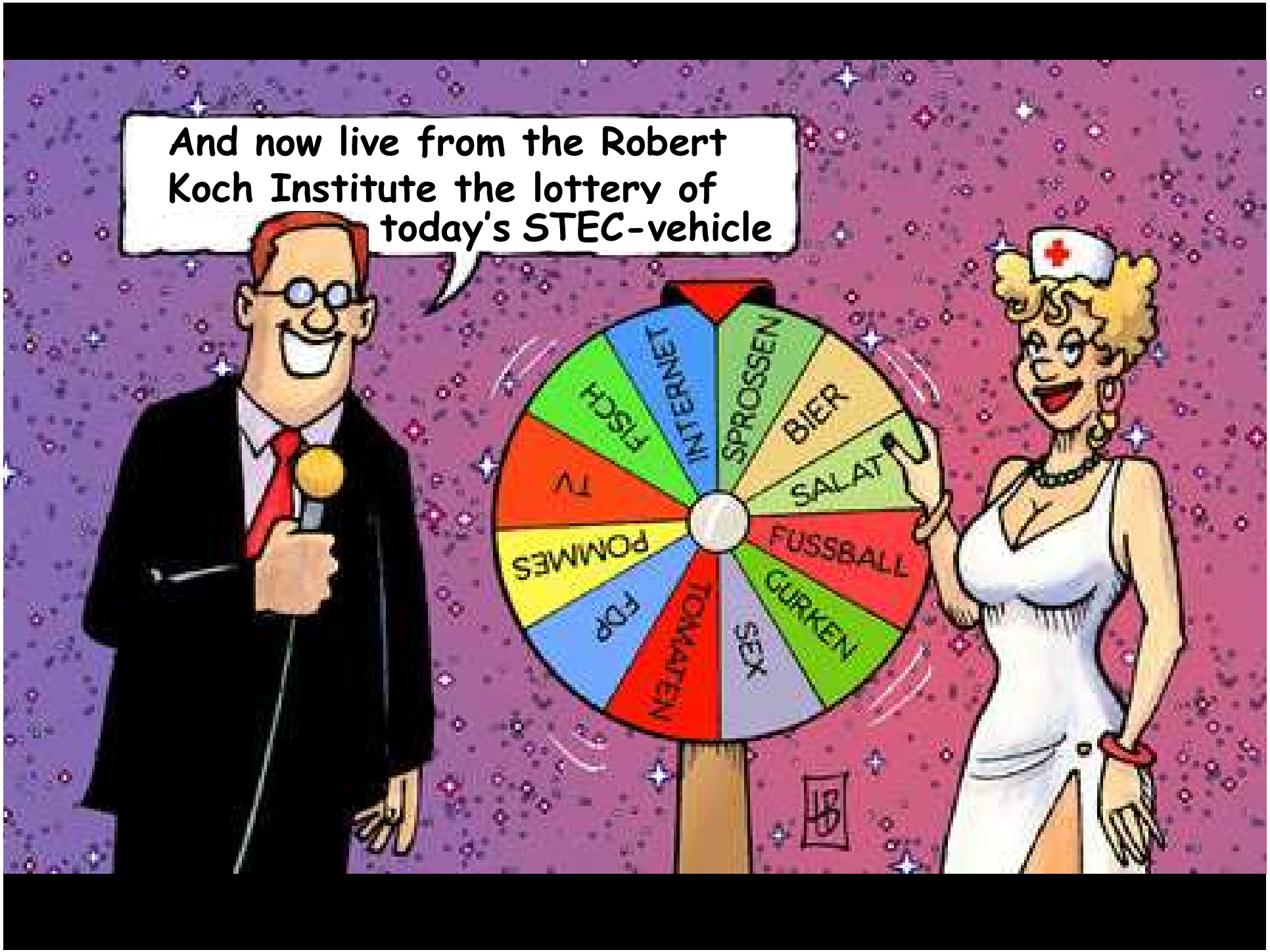
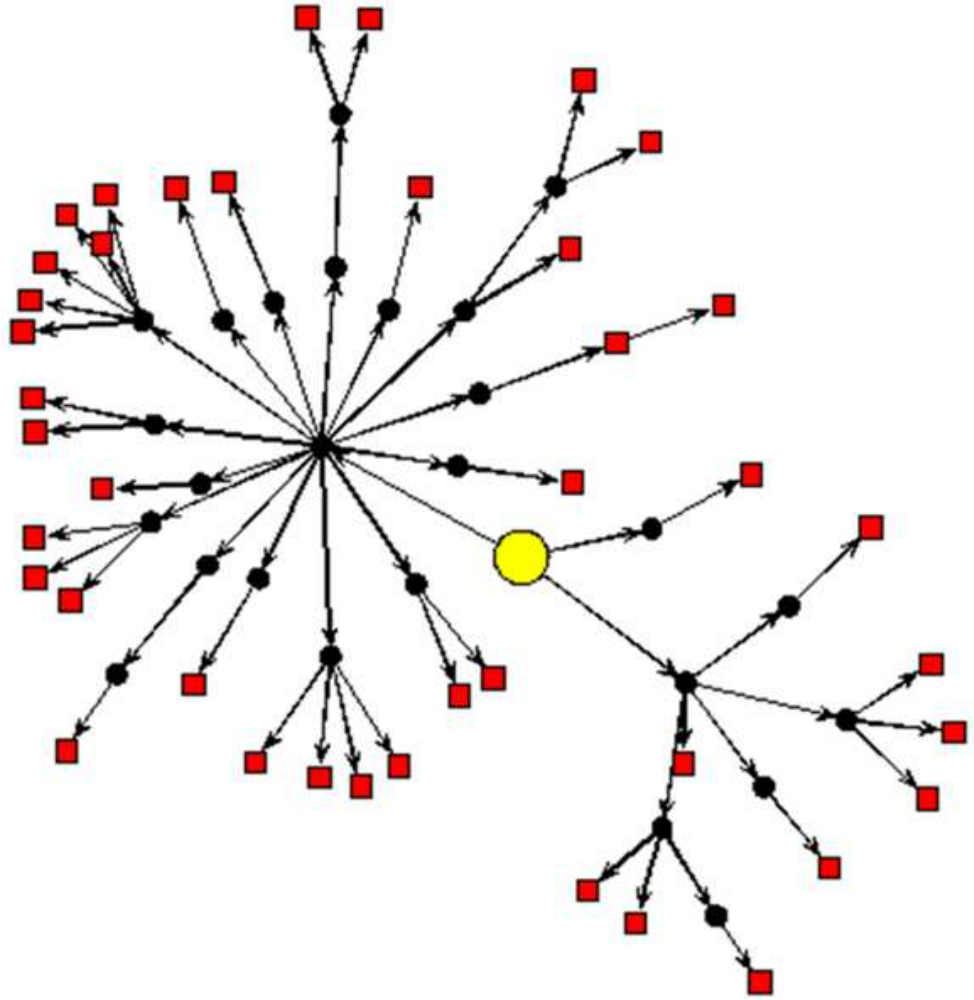

And now live from the Robert Koch Institute the lottery of today's STEC-vehicle
SPROSSEN
BIER
SALAT
FUSSBALL
GURKEN
SEX
TOMATEN
FDP
POMMES
TV
FISCH
INTERNET

Distribution channels of food enterprise A in Lower Saxony (yellow) to 26 sprout distribution points (black) and 41 clusters (red), STEC / HUS outbreak, Germany, 2011.



Buchholz et al.. New England Journal of Medicine, 2011

Retrospective projection of timing of exposure

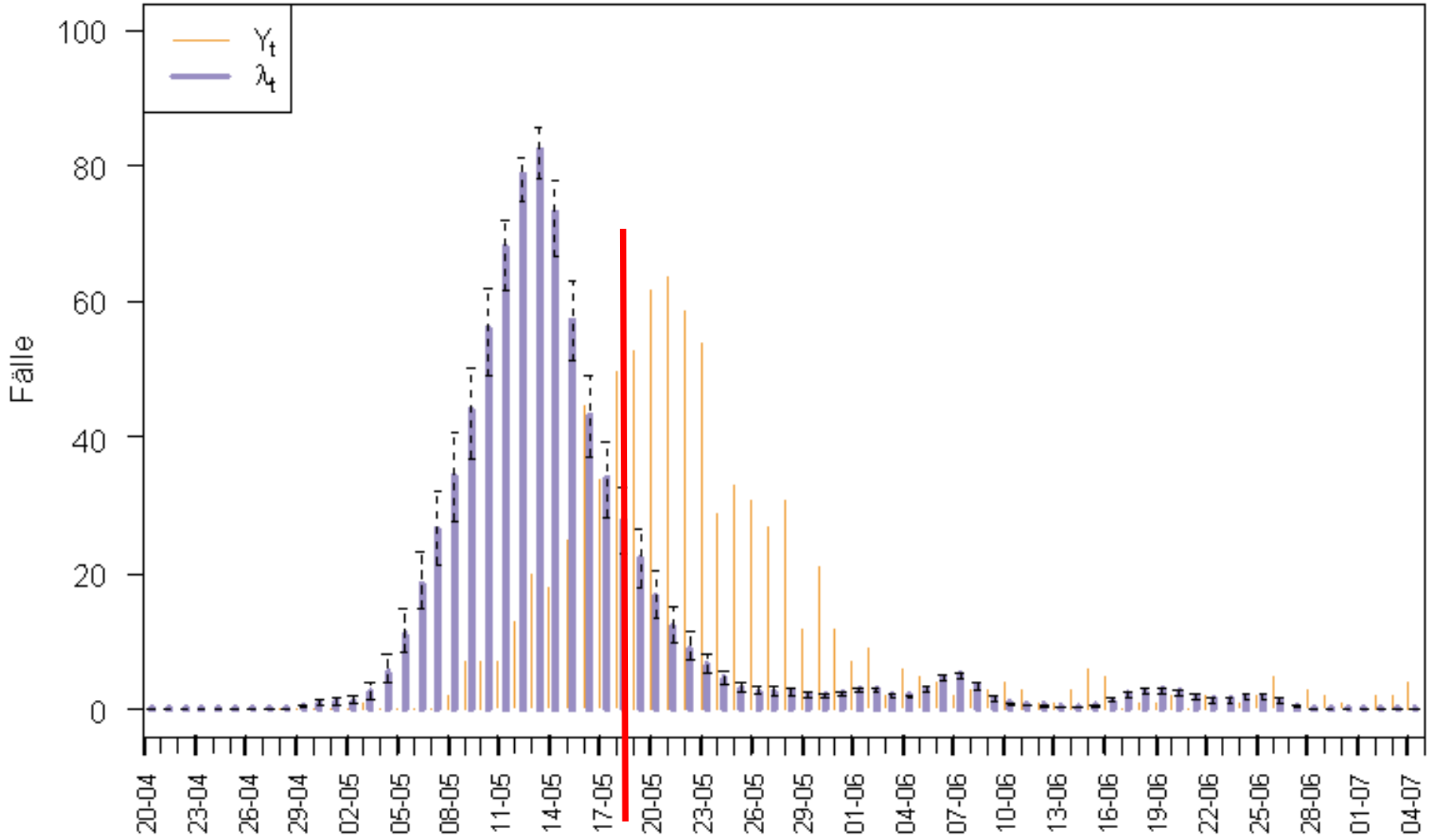
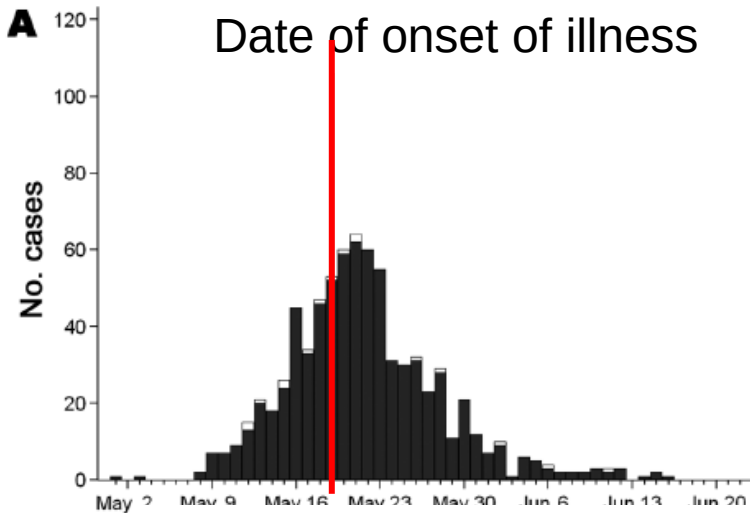


Abbildung 6: Rückprojektion der täglichen Erkrankungsbeginne auf Expositionszeitpunkte. Die dünne orange Kurve Y_t zeigt die tatsächlich beobachteten Erkrankungsbeginne, die dicke blaue Kurve z_t zeigt die geschätzte Anzahl Expositionen pro Tag (inkl. 95% Konfidenzintervalle).

Source: RKI. Sachstandsbericht EHEC/HUS O104:H4 Ausbruch, 7.9.2011

Epidemiological curves at different points in time



Source: Altmann et. al, Emerg Infect Dis. 2011 Oct

Timeline of EHEC outbreak and response

May 9th	Increase in HUS cases from 0-2/d to 9/d
May 21st	63 HUS cases/day
May 24th	EHEC telephone hotline of the Germany Society of Nephrology
May 25th	First HUS patient treated with eculizumab
May 27th	EHEC-HUS Register online (www.ehec-register.de)
May 31st	Suggestions of the German Society of Nephrology on the treatment with eculizumab
June 1st	EHEC-HUS Registry English version (www.ehec-hus.net)
June 2nd	Complete genome analysis of the outbreak strain available online
June 9th	Immunoadsorption with protein A columns for HUS patients with severe neurological involvement reported
June 24th	France reports a cluster of eight patients with bloody diarrhoea, seven have developed HUS,

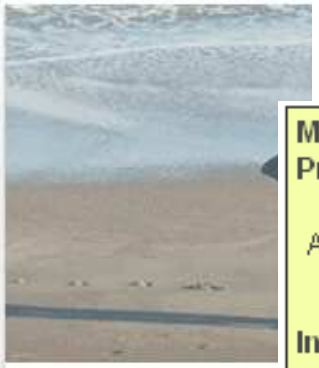
Fig. 1. Timeline of EHEC outbreak and response.

The German 2011 epidemic of Shiga toxin-producing E. Coli—the nephrological view; The German EHEC-HUS Registry, J. Kielstein, Nephrol Dial Transplant (2011)

Clinic

- Phase 1
  - most: bloody diarrhea, some: watery, seldom: no diarrhea
- Phase 2
  - 1/3 signs of thrombotic microangiopathy (TMA) 3 – 5 days
- Phase 3: after another 3 – 10 days
  - Neurological signs (some patients re-hospitalized) from mild disorientation, qualitative and quantitative alterations of consciousness, double vision, dysphasia, hyperreflexia and apraxia to loss of adverse effects reflexes or repeated epileptic seizures requiring intubation → no neuroradiological signs
  - Majority also psychiatric abnormalities

Deutsche Gesellschaft
für Nephrologie



Eculizumab can be considered id after 0-5 Therapeutic Plasma Exchanges (TPE) in patients with EHEC associated HUS the following criteria are met:

Inclusion

Meningokokk
Prophylaxe n

Azithromycin

Initiierung de

(Tag 0 – 7 - 1

mit jeweils 9

!! CAVE !! bei
einer Stunde

Exclusion criteria

1. **Identified to be Shiga toxin (-) or EHEC (-)**
2. **Previous treatment with eculizumab**
3. **Pregnancy or lactation**
4. **Known Complement regulatory mutation or family history**
5. **Unresolved meningococcal/gonorrhea/pneumococcal infection**
6. **Unresolved Sepsis**

Recommended minimum laboratory parameter

daily:

- CBC
- ceatinine
- LDH

3 x / week:

- shistocytes
- free hemoglobin level
- CRP
- urin-Status (Stix)

ice on the use of Ecilizumab

4.
Acute Kidn

Def.[1] : > 3-facher Kreatininanstieg oder Serum-Kreatinin > 4 mg/dl mit einem akuten Anstieg ≥ 0,5 mg/dl und Urin-Ausscheidung <0,3 ml/kg/h für 24 h oder Anurie für 12 h

5.
Venous or arterial thrombembolic events

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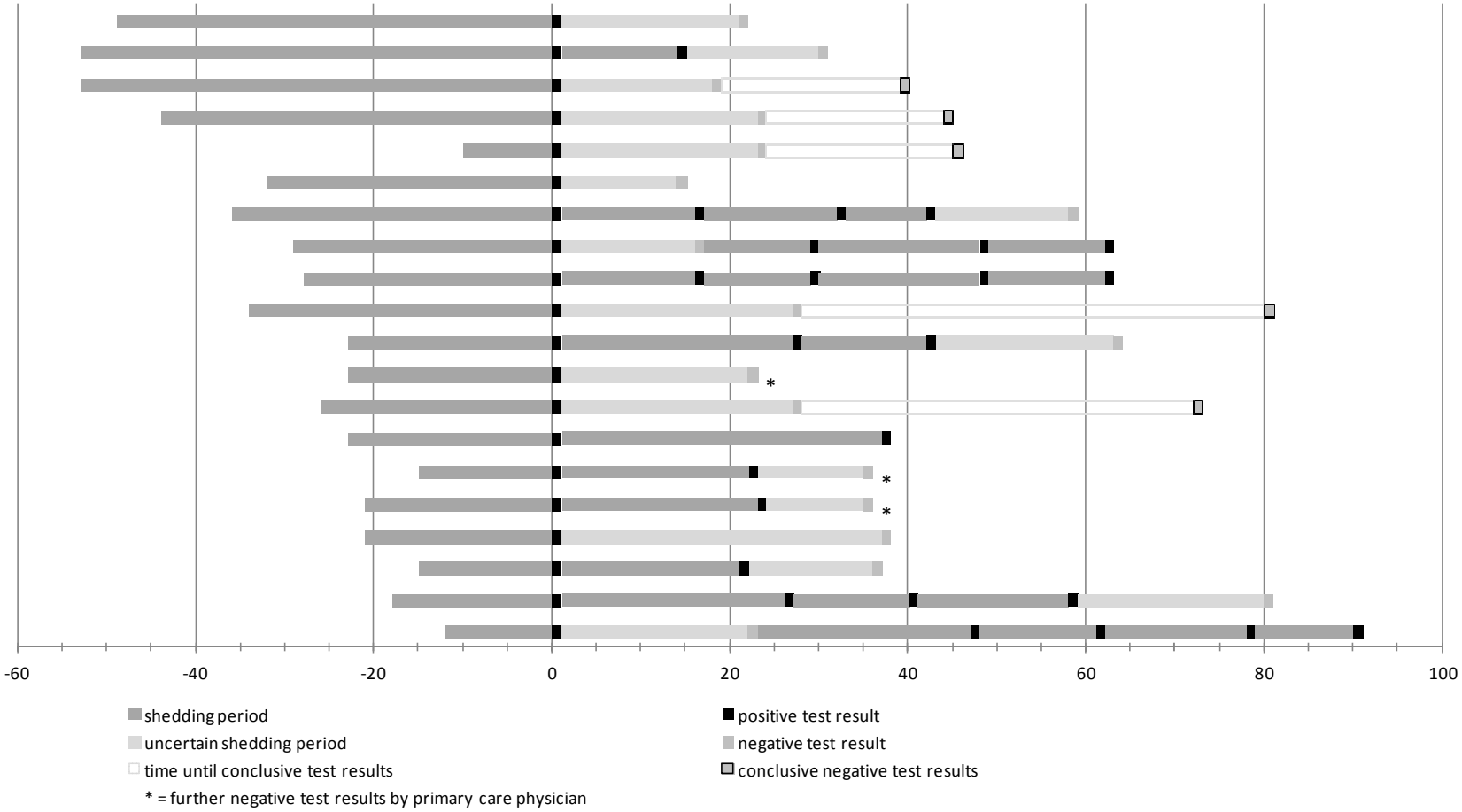
German Society of Nephrology

- 70 centers
- 483 patients included in HUS-Registry
- Questions:
  - Meaningfullness of therapeutic Plasma Exchange (TPE)
  - Effectiveness of EZULICUMAB

Follow up study in Hamburg and Lübeck

- Right use of antibiotics
  - Basically if
  - Which
  - When
- Risk factors for severe cases
- Long term complications of HUS

Days followed since disease onset and sampling results per carrier by duration of shedding, prospective cohort study part, household study; Shiga-toxin producing *E. coli* outbreak, Germany, 2011.



Conclusion

- **The largest outbreak of HUS worldwide**
  - > 3,800 illnesses, 53 deaths in Germany
  - Regional outbreak with international implications

- **Clinical treatment**
  - Large surge capacity in hospitals
  - Therapeutic Plasma Exchange (TPE)?
  - EZULICUMAB?
  - Antibiotics?

- **Pathogen detection:**
  - Rapid identification of pathogen
  - Most laboratories have only applied shigatoxin-detection
  - So far no detection in untouched food sample

Conclusion

- **Epidemiology**
  - Low potency of transmission
  - Long duration of shedding
  - Only few asymptomatic carriers
  - So far no evidence of endemic establishment

- **Questions**
  - Outbreak France → Link seeds from UK
  - Outbreak Turkey → Link?
  - Source Agypt?

- **Communication**
  - Remains a challenge

Explaining and Proclaiming Uncertainty: Risk Communication Lessons from Germany's Deadly *E. coli* Outbreak

by Peter M. Sandman and Jody Lanard

Nobody likes uncertainty. Everybody on the receiving end of risk communications prefers those communications to be definitive, not tentative.

In 2004, one of us (Peter) wrote a column entitled "Acknowledging Uncertainty." It has two main sections: a brief list of tips on how to sound uncertain, and a more complex protocol for "being precise about uncertainty" – for deciding how uncertain you want to sound and then finding words that sound that way. The 2004 column goes into detail about the biases and pressures that lead risk communicators to sound overconfident. But we now think it greatly underestimates the difficulty of successfully communicating uncertainty, as opposed to merely "acknowledging" it – which may get it onto the record but doesn't necessarily get it into the minds of the audience, where it needs to be.

This column is about the need to proclaim uncertainty, not just acknowledge it. !

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RKI EHEC-Infektionen

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- Infektionsschutz
- Infektionskrankheiten A - Z
- EHEC-Infektionen
- Forschung
- Service

Suche

Suchbegriff

Aktuelle Themen

- EHEC-Bericht
- Wissenschaftliche Veröffentlichungen
- Fragebögen und Studien des RKI
- EM-Aufnahme von EHEC O104:H4

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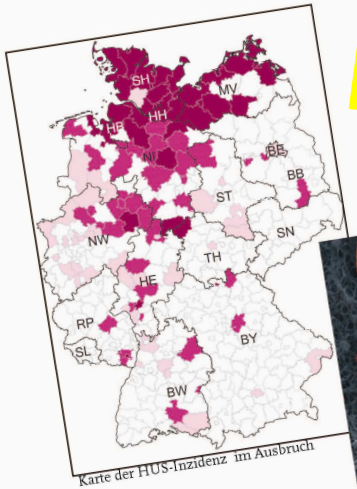
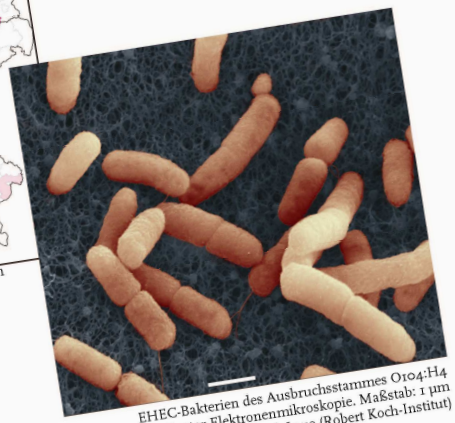
Abschließende Darstellung und Bewertung der epidemiologischen Erkenntnisse im

EHEC O104:H4 Ausbruch
Deutschland 2011

Soon available in English



Karte der HUS-Inzidenz im Ausbruch


EHEC-Bakterien des Ausbruchsstammes O104:H4
Raster-Elektronenmikroskopie. Maßstab: 1 µm
Quelle: Holland, Laue (Robert Koch-Institut)

Publications

Frank C, Faber MS, Askar M, Bernard H, Fruth A, Gilsdorf A, Höhle M, Karch H, Krause G, Prager R, Spode A, Stark K, Werber D, on behalf of the HUS investigation team. Large and ongoing outbreak of haemolytic uraemic syndrome, Germany, May 2011. **Euro Surveill**. 2011;16(21):pii=19878.

Askar M, Faber MS, Frank C, Bernard H, Gilsdorf A, Fruth A, Prager R, Höhle M, Suess T, Wadl M, Krause G, Stark K, Werber D. Update on the ongoing outbreak of haemolytic uraemic syndrome due to Shiga toxin-producing Escherichia coli (STEC) serotype O104, Germany, May 2011. **Euro Surveill.** 2011;16(22):pii=19883.

Wadl M, Rieck T, Nachtnebel M, Greutélaers B, an der Heiden M, Altmann D, Hellenbrand W, Faber M, Frank C, Schweickert B, Krause G, Benzler J, Eckmanns T, on behalf of the HUS surveillance and laboratory team. Enhanced surveillance during a large outbreak of bloody diarrhoea and haemolytic uraemic syndrome caused by Shiga toxin/verotoxin-producing Escherichia coli in Germany, May to June 2011 . **Euro Surveill.** 2011;16(24):pii=19893.

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Bielaszewska M, Mellmann A, Zhang W, Köck R, Fruth A, Bauwens A, Peters G, Karch H. Characterisation of the Escherichia coli strain associated with an outbreak of haemolytic uraemic syndrome in Germany, 2011: a microbiological study. **Lancet Infect Dis** 2011

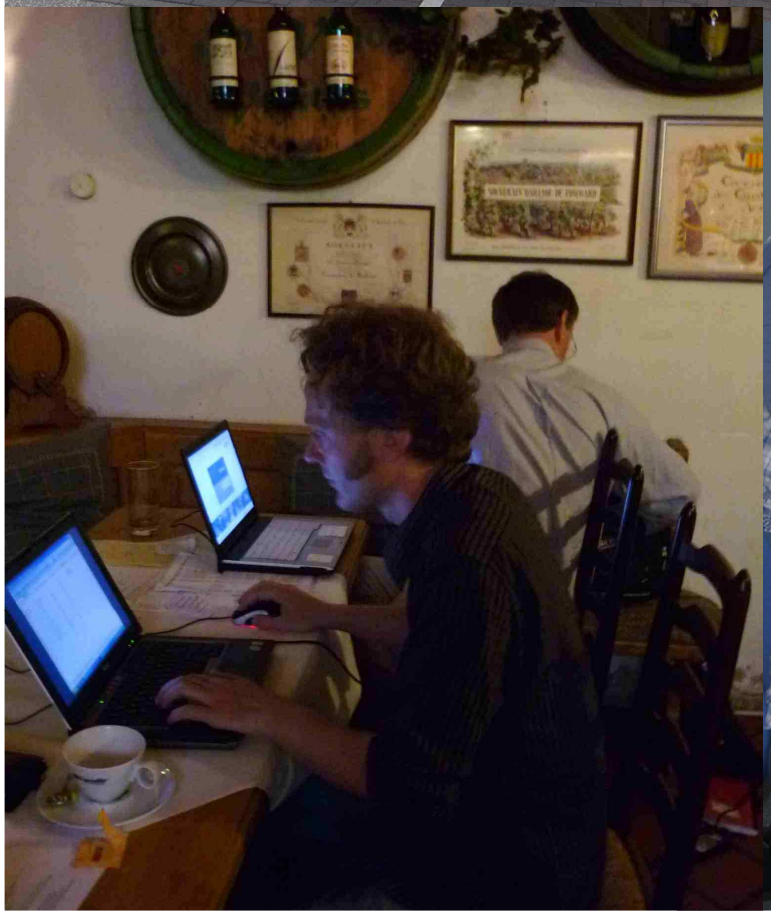
Mellmann A, Harmsen D, Cummings CA, Zentz EB, Leopold SR, et al. Prospective Genomic Characterization of the German Enterohemorrhagic Escherichia coli O104:H4 Outbreak by Rapid Next Generation Sequencing Technology. **PLoS ONE** 2011;6(7): e22751.

Altmann M, Wadl M, Altmann D, Benzler J, Eckmanns T, Krause G, et al. Timeliness of surveillance during outbreak of Shiga toxin–producing Escherichia coli, Germany, 2011. **Emerg Infect Dis.** 2011 Oct; [Epub ahead of print]

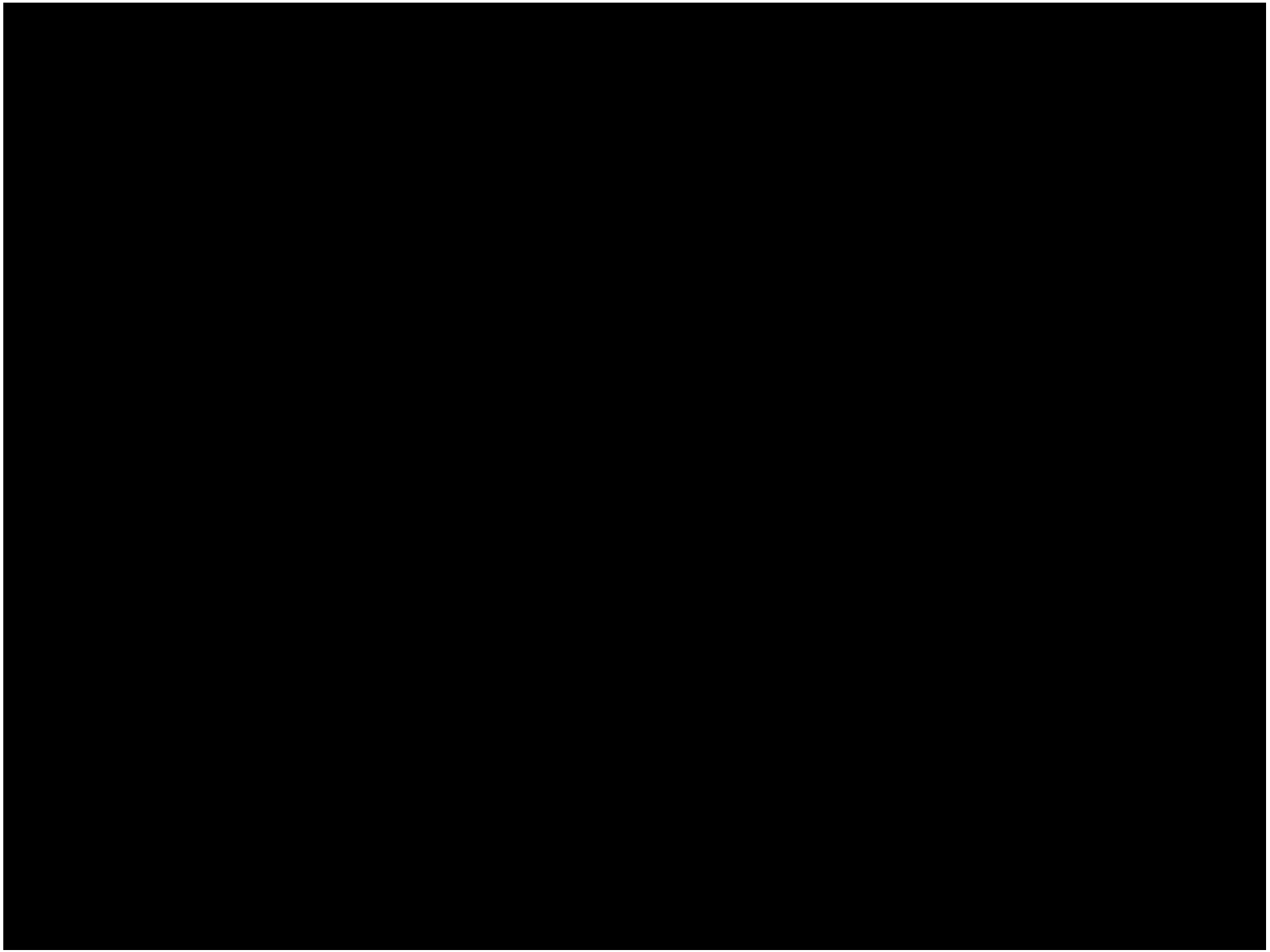
Buchholz U, Bernard H, Werber D, Böhmer M, Remschmidt C, Wilking, H, Deleré Y, an der Heiden M, Adlhoch C, Dreesman J, on behalf of the NLGA HUS investigation team, Ehlers J, Ethelberg S on behalf of the Danish HUS investigation team, Faber M, Frank C, Fricke G on behalf of the Task Force EHEC at BVL, Greiner M, Höhle M, Ivarsson S, on behalf of the Swedish HUS investigation team, Jark U, Kirchner M, Koch J, Krause G, Luber P, Rosner R, Stark K, Kühne M on behalf of the LAVES HUS investigation team; and the RKI HUS Investigation Team (2011). Escherichia coli O104:H4 Associated with Sprouts – Germany, 2011. **New Engl J Med**. 2011

Our special thanks go to …

- Patients and relatives
- Study participants
- Restaurant owners and cooks
- Doctors and staff in hospitals
- State and local health authorities
- Food safety authorities
- Foreign national health authorities
- ECDC, EFSA, WHO, …




Coca-Cola
DELL



Back up slides

Microbiological profile

- **Shigatoxin 1:** **- (negative)**
- **Shigatoxin 2 (vtx2a) :** **+ (positive)**
- **Intimin (eae) :** **- (negative)**

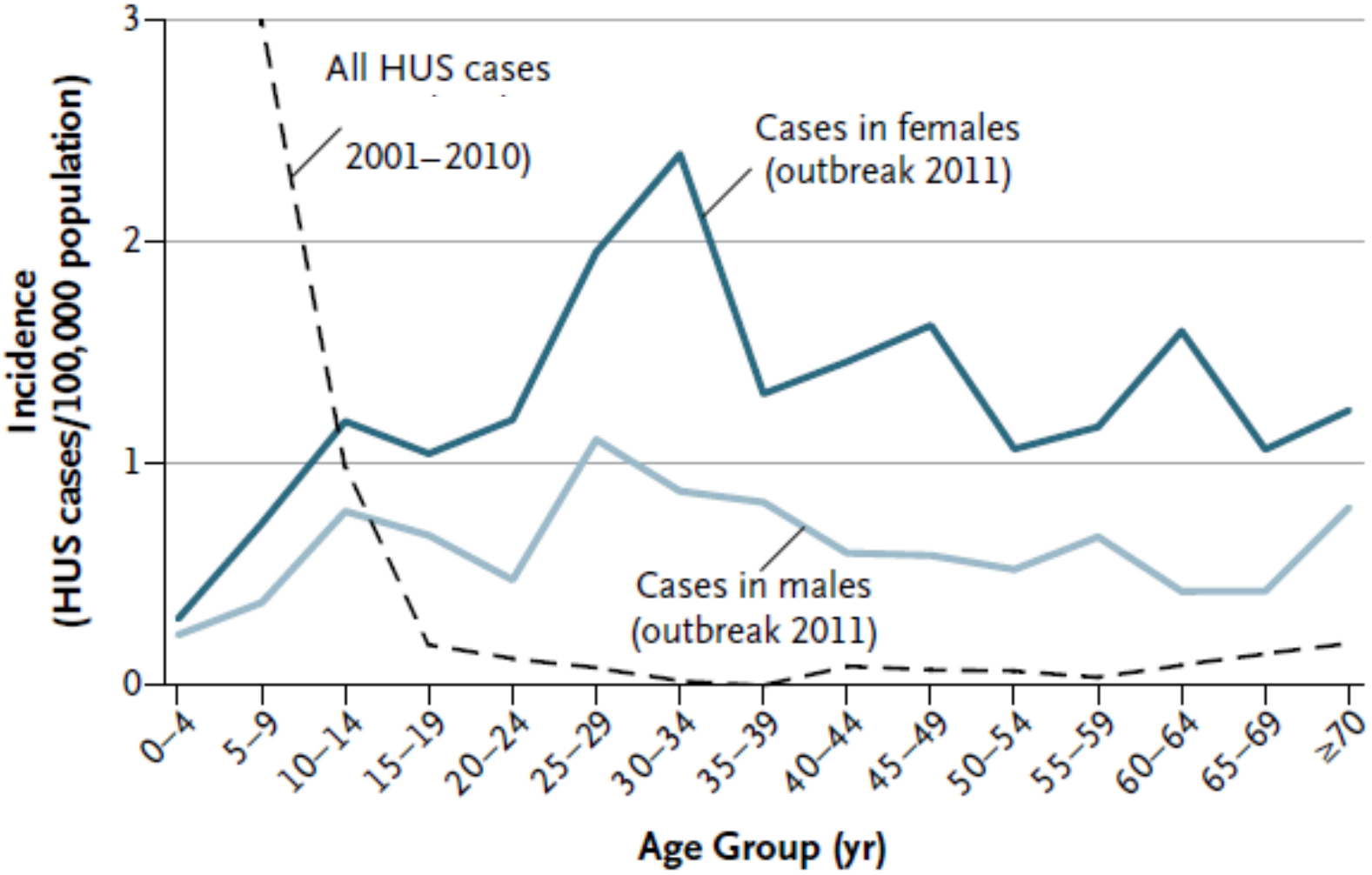
- Enterohemolysin : - (negative)

- EaggEC virulence plasmid !!
- aatA-PCR: + (positive) (ABC-transporter protein gene)
- aggR-PCR: + (positive) (master regulator gene of Vir-plasmid genes)
- aap-PCR: + (positive) (secreted protein dispersin gene)
- aggA-PCR: + (positive) (AAF/I-fimbral subunit-gene) *
- aggC-PCR: + (positive) (AAF/I-fimbral operon-gene) *

* Fimbriae expressed by O104:H4 strain HUSEC 041 (www.rki.de) (RKI-01-09591) are of type AAF/III (Prager, Fruth, and Tschäpe poster abstract EHEC Workshop 2007).

Reported HUS incidence by age and sex

(Status as of June 17, 2011)



Source: Frank C, Werber D, Cramer JP et al. NEJM 2011

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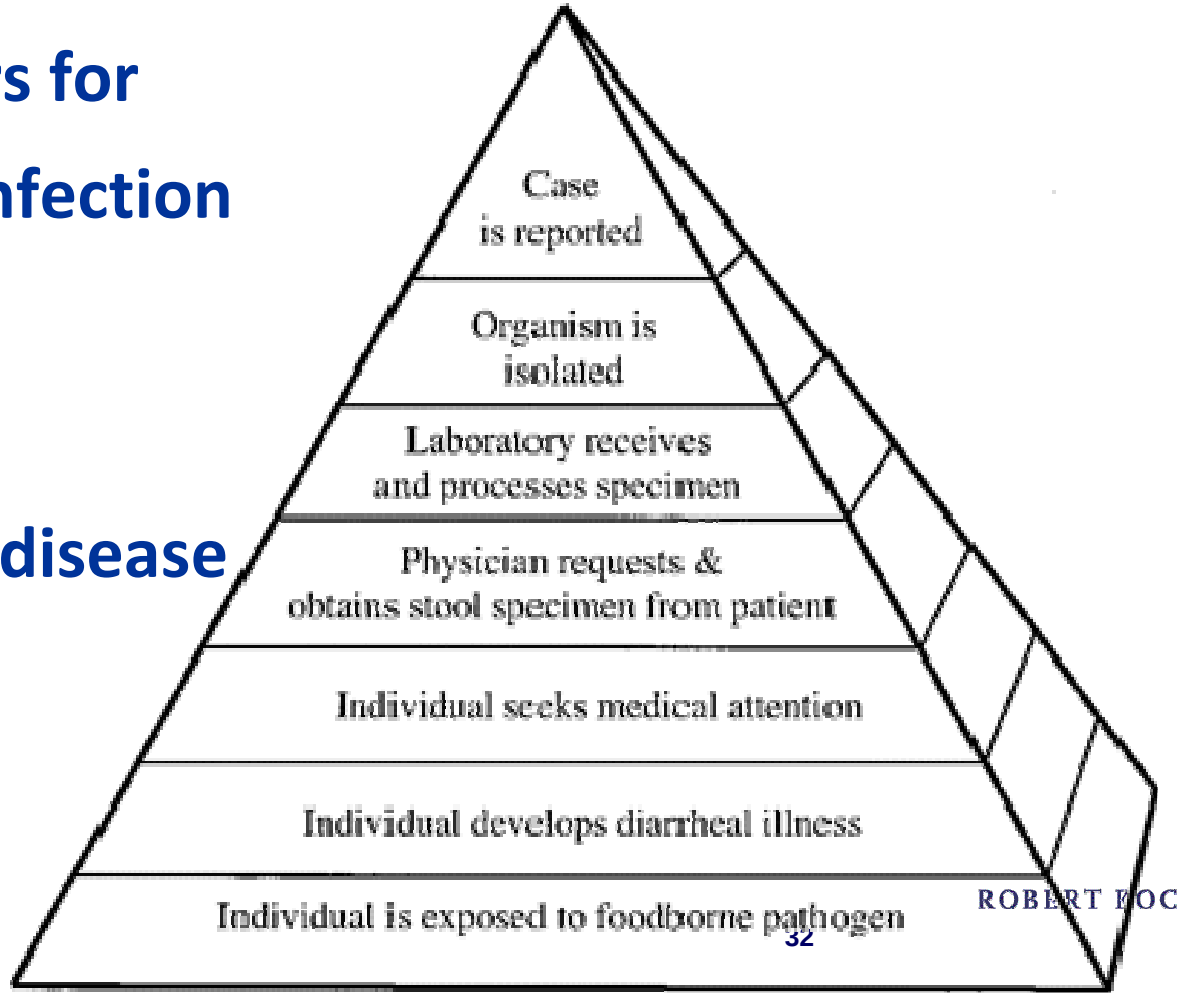
Open questions: epidemiology

- Duration of shedding
- Secondary transmission from human to human
- Risk factors for
  - EHEC Infection
  - HUS
  - Death
- Burden of disease



Similar outbreaks

	Japan, 1996 EHEC O157 (Radish sprouts)	USA, 2006 EHEC O157 (Spinach)	USA, 2008 *S. Saintpaul* (Chile shoots)	Deutschland, 2011 EHEC O104 (Sprouts)
Number of cases	~12.000	~210	~1.500	3.842
Case fatality	3-11	3	2	53
Time from first Infection till Outbreak detection	>7 weeks	~3 weeks	~4 weeks	~2 weeks
Time from identification of outbreak Till identification of Source of infection	>4 weeks	~5 days	~7 weeks	~3 weeks
Duration of outbreak	~12 weeks	~6 weeks	~16 weeks	~8 weeks

Open questions: pathogen

- Origin of the pathogen
  - Reservoir
- Food safety
  - Prevalence of EHEC in raw vegetables
  - Detectability of EHEC in sprouts

The sprout question - "stealth vehicle"

Germany

- Consumption of sprouts was confirmed…
  - First explorative interview: 3/12 (25%) HUS patients
  - All explorative interviews : 17/57 (30%) HUS patients
  - Case-Control-Study 4 (CCS4):
    - 6/24 (25%) HUS/EHEC cases
    - 7/80 (9%) controls
  - Repeated interview with CCS4, after sprouts discussed in the media:
    - 3/8 (38%) re-interviewed cases changed initial answer from “no” to “yes”
    - None of 37 re-interviewed controls changed its initial answer

Denmark

- None of the cases recalled eating sprouts

France

- Cases only remembered sprout consumption in follow-up interviews

(WHO 2008: Foodborne disease outbreaks : guidelines for investigation and control ISBN 978 92 4 154722 2)

Sources: RKI. Sachstandsbericht EHEC/HUS O104:H4 Ausbruch, 7.9.2011; Gault G et al., Euro Surveill. 2011;16(26):pii=19905; Communication with Danish and Swedish authorities.

Retrospective projection of timing of exposure

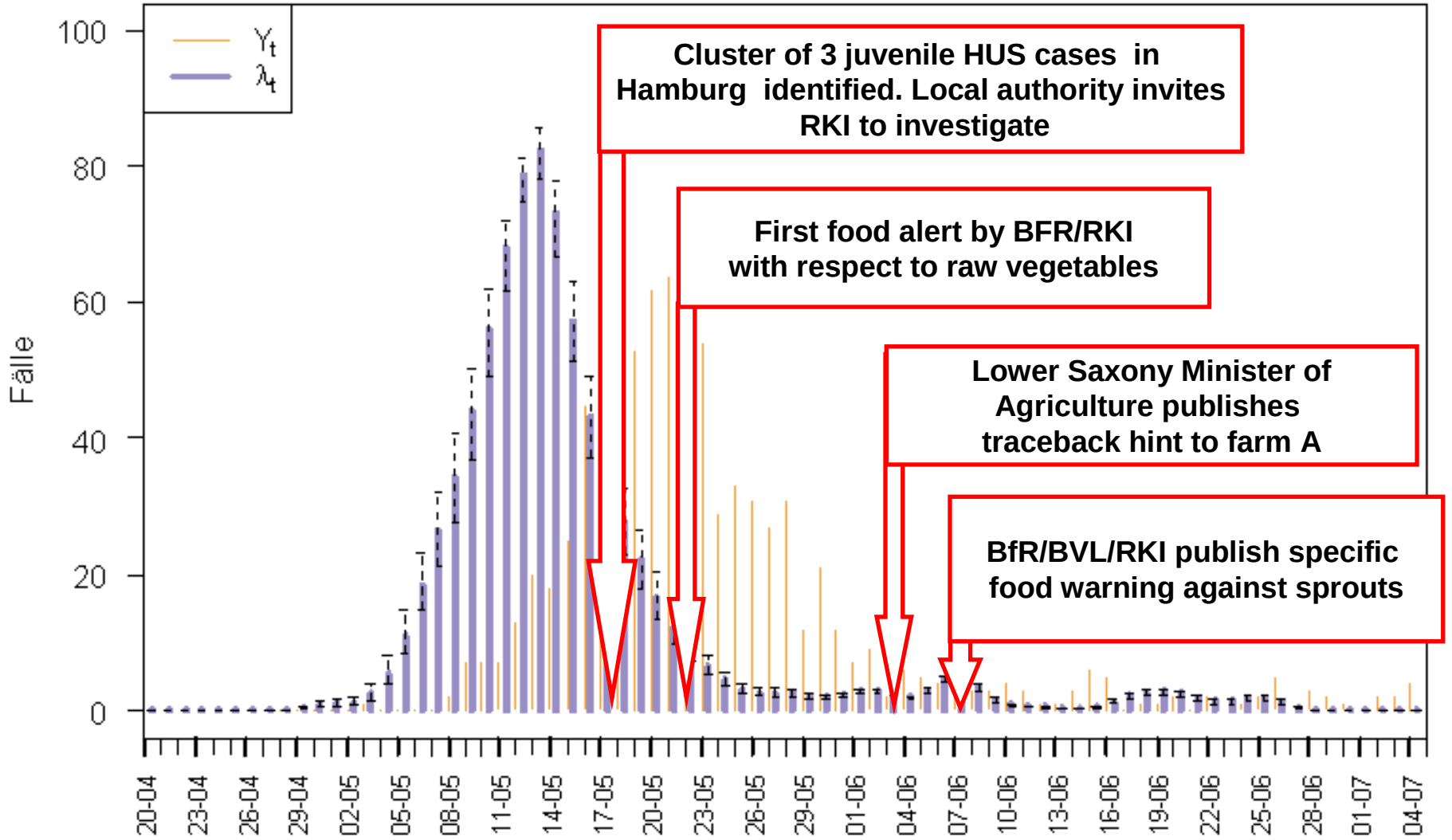


Abbildung 6: Rückprojektion der täglichen Erkrankungsbeginne auf Expositionszeitpunkte. Die dünne orange Kurve Y_t zeigt die tatsächlich beobachteten Erkrankungsbeginne, die dicke blaue Kurve z_t zeigt die geschätzte Anzahl Expositionen pro Tag (inkl. 95% Konfidenzintervalle).

Source: RKI. Sachstandsbericht EHEC/HUS O104:H4 Ausbruch, 7.9.2011

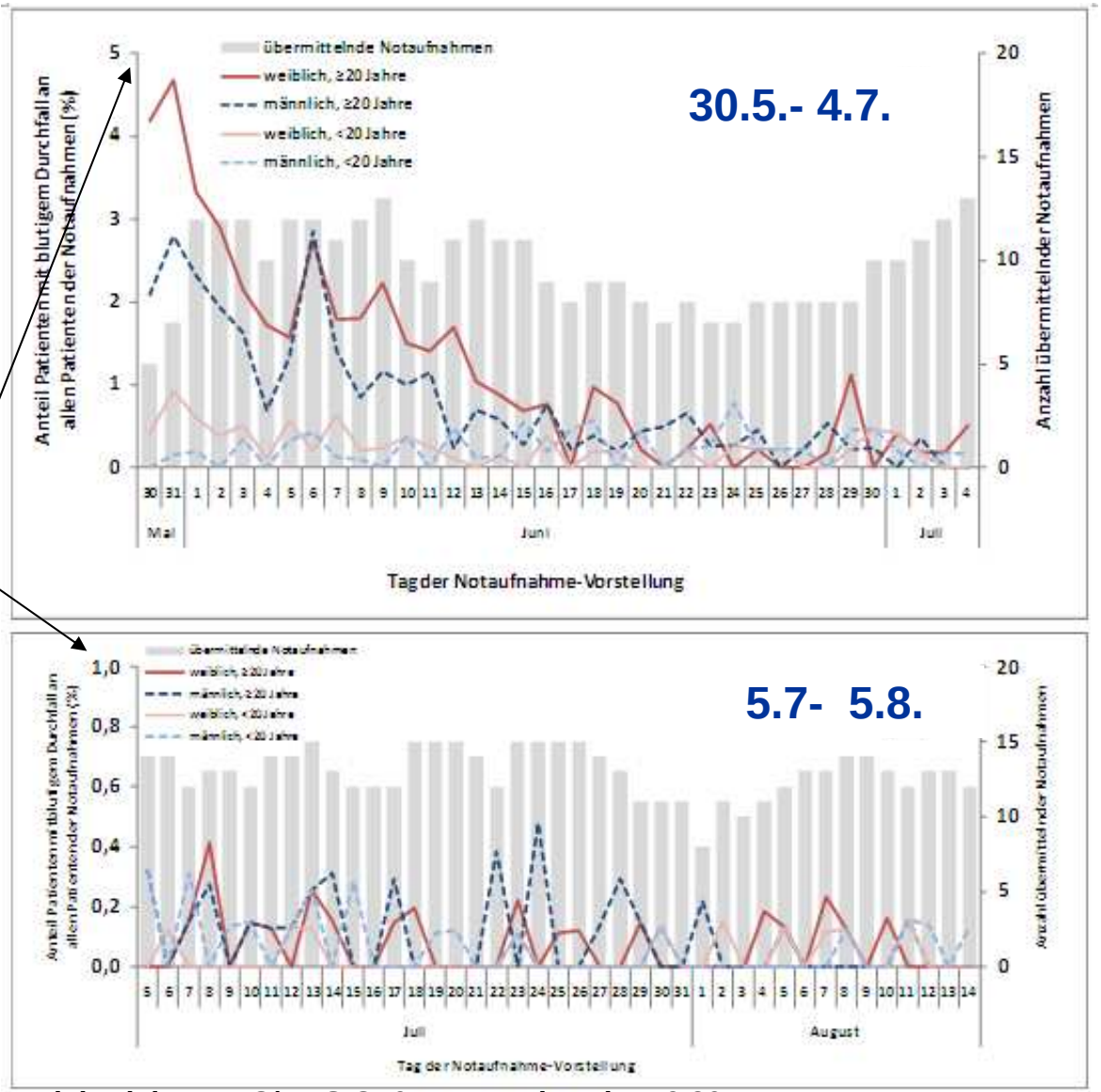
Reporting delays

(Date of onset of illness)

County-level incidence

(Cumulative, date of onset of illness)

Proportion of emergency room patients with bloody diarrhea by age and gender (n = 747)



Different scales depicted

Source: RKI. Sachstandsbericht EHEC/HUS O104:H4 Ausbruch, 7.9.2011

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