Aus der Klinik für Pädiatrie
mit dem Schwerpunkt Pneumologie und Immunologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Automated case classification of neurologic adverse events at the point-of-care and enhanced virologic surveillance – new avenues towards quality improvement and precision medicine

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Patrick Erich Obermeier
aus Darmstadt

Datum der Promotion:
02.03.2018

In Memoriam

Prof. Dr. Gerhard Gaedicke

Table of Content

Abbreviations 4
Abstract (in German and English) 5
1 Introduction 9
2 Methods 10
2.1 The Meningitis Surveillance at Charité (MenSCh) Cohort 10
2.2 Implementation of digital case classification at the point-of-care 11
2.3 Statistics 12
2.4 Standard protocol approvals 12
3 Results 13
3.1 Unbiased syndromic surveillance for aseptic meningitis, encephalitis, myelitis, and ADEM using the VACC-Tool at the point-of-care 13
3.1.1 Key features in patients classified as aseptic meningitis, encephalitis, and ADEM 13
3.1.2 Comparison between retrospective case classification and prospective case classification using the VACC-Tool 14
3.1.3 Comparison between ICD-10 codes and prospective case classification using the VACC-Tool 15
3.2 Key clinical features in parechovirus positive patients 15
3.3 Using the VACC-Tool to facilitate individualized medicine – a case of ADEM following human parechovirus infection 16
4 Discussion 17
5 References 22
Affidavit 25
Declaration of Contributions 26
Enabling Precision Medicine with Digital Case Classification at the Point-of-Care 27
Commentary by Marinka Twilt 33
Human Parechovirus Infections Associated with Seizures and Rash in Infants and Toddlers 35
Acute Disseminated Encephalomyelitis After Human Parechovirus Infection 42
Curriculum Vitae 46
Publications and Presentations 48
Acknowledgements 56

Abbreviations

ADEM – Acute Disseminated Encephalomyelitis

CD – Cluster of Differentiation

CDISC – Clinical Data Interchange Standards Consortium

CNS – Central Nervous System

CSF – Cerebrospinal Fluid

HSV – Herpes Simplex Virus

ICD – International Catalog of Diseases

ICH – International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IRB – Institutional Review Board

KL – Kullback-Leibler-Divergence

MenSCh – Meningitis Surveillance at Charité

MRI – Magnetic Resonance Imaging

NPA – Negative Percent Agreement

ORA – Overall Rate of Agreement

PMI – Precision Medicine Initiative

PPA – Positive Percent Agreement

QM – Quality Management

RNA – Ribonucleic Acid

RT-PCR – Reverse Transcription Polymerase Chain Reaction

U.S. – United States (of America)

VACC-Tool – Vienna Vaccine Safety Initiative Automated Case Classification-Tool

ViVI – Vienna Vaccine Safety Initiative

Abstract (in German, 398 words)

Einleitung: Die zeitnahe und konsequente Erfassung neuroinfektiologischer Krankheitsbilder stellt ganz besonders bei Kindern eine Herausforderung dar. Aseptische Meningitis, Encephalitis und akute disseminierte Encephalomyelitis (ADEM) können sowohl durch Infekte hervorgerufen werden sowie, wenn auch seltener, durch Arzneimittel- oder Impfnebenwirkungen. Für eine lückenlose Surveillance müssen diagnostische Kriterien vereinheitlicht werden. Hierzu haben sich Expertengremien auf internationale Falldefinitionen geeinigt, die unabhängig vom Auslöser der Symptome universell einsetzbar sind. Wenn diese Kriterien rückwirkend angewandt werden, bleiben jedoch solche Fälle ungeklärt, bei denen relevante Parameter nicht bereits in der Routineversorgung erfasst wurden. Die vorliegende Arbeit soll klären, inwiefern der Einsatz mobiler Applikationen auf PCs und Tablet-Computern zu einer standardisierten und vollständigen Erfassung klinischer Fälle beitragen kann.

Methodik: Die Arbeit erfolgte im Rahmen eines Qualitätsmanagementprogramms der Charité-Kinderklinik in Zusammenarbeit mit dem Robert-Koch-Institut. Hierbei wurde das VACC-Tool (ViVI Automated Case Classification-Tool) eingesetzt, das sowohl als App wie auch als Web-User Interface zur Verfügung stand. Das VACC-Tool hilft dabei sämtliche Parameter direkt am Patienten zu erfassen, die für die publizierten Falldefinitionen „Aseptische Meningitis“, „Encephalitis“, „Myelitis“ und „ADEM“ relevant sind. Die VACC-Tool-Resultate wurden mit der retrospektiven Anwendung derselben Fallkriterien auf den jeweiligen Entlassbrief verglichen sowie mit den darin dokumentierten ICD-Codes. Sofern verfügbar, wurden zusätzlich Stuhlproben im Robert-Koch-Institut auf humane Parechoviren getestet.

Ergebnisse: Von November 2010 bis Juni 2013 wurden von 68.921 Patienten in der Charité-Kinderrettungsstelle 11.575 Patienten stationär aufgenommen. Am Qualitätsmanagementprogramm nahmen insgesamt 521 Patienten teil (Durchschnittsalter 7,6 Jahre). Mittels VACC-Tool konnten 180 (34,6 %) Fälle entweder als aseptische Meningitis, Encephalitis und/oder ADEM klassifiziert werden, in 194 Fällen konnten alle vier Diagnosen sicher ausgeschlossen werden. Für 147 Patienten blieb die Klassifizierung aufgrund mangelnder Labor-, elektrophysiologischer oder radiologischer Untersuchungsbefunde zunächst offen. Im Vergleich dazu wären bei der retrospektiven

Auswertung der Entlassbriefe insgesamt 33 Fälle übersehen worden, mittels ICD-10 Codes sogar 116 Fälle. Die Untersuchung im Robert-Koch-Institut ergab, dass positive Parechovirusnachweise im Stuhl von Patienten unter 4 Jahren signifikant häufig mit Krampfanfällen und Hautausschlägen assoziiert waren. Zusätzlich konnte auf diesem Wege der bisher erste Fall einer ADEM infolge humaner Parechovirusinfektionen beschrieben werden.

Schlussfolgerung: Der Einsatz digitaler Medien kann Ärzte dabei unterstützen, die richtigen Fragen zur rechten Zeit zu stellen, nämlich während der Patient noch vor Ort ist. Eine noch höhere Klassifizierungsrate ließe sich dann erreichen, wenn der Arzt bei bestätigtem Verdacht noch an relevante diagnostische Testverfahren erinnert würde. Hierdurch ließe sich die Umsetzung internationaler Konsensus-Kriterien vereinheitlichen, mit erheblichen Qualitätsverbesserungen für die Praxis, für klinische Studien und die Surveillance im Robert-Koch-Institut.

Abstract (in English, 388 words)

Introduction: The timely and unbiased classification of neurologic adverse events is challenging, especially in children. Aseptic meningitis, encephalitis, and acute disseminated encephalomyelitis (ADEM) may be triggered by infections, but also represent adverse events following immunization or drug administration. For a systematic surveillance of adverse events, uniform case criteria have been defined irrespective of the trigger of an event. When case criteria are applied retroactively, some cases may remain 'indeterminate' if pertinent clinical data were missing in routine records. The present work explores the use of mobile applications for personal and tablet computers to increase the yield of standardized case classification.

Methods: The present work was conducted in the context of a quality management program at the Charité Department of Pediatrics in collaboration with the Robert-Koch-Institute. The VACC-Tool (Vienna Vaccine Safety Initiative Automated Case Classification Tool) was made available as a mobile application or web-user interface, allowing staff to capture all clinical parameters required by published case definitions for aseptic meningitis, encephalitis, myelitis, and ADEM. VACC-Tool assessments were compared to ICD-codes and to retrospective application of the same definitions to medical records. If available, stool samples were tested for human parechoviruses at the Robert-Koch-Institute.

Results: From November 2010 – June 2013, 68,291 patients attended the pediatric emergency room and 11,575 were hospitalized. Of these, 521 patients participated in the program (mean age 7.6 years). Using the VACC-Tool, 180 cases (34.6 %) were classified as aseptic meningitis, encephalitis, and/or ADEM, 194 cases were ruled-out for any of the above-mentioned diagnoses. For 147 patients, classification remained 'indeterminate' because of missing laboratory, electrophysiology, or neuroimaging data. In comparison, 33 cases were missed by retrospective analysis of discharge summaries and 116 cases by ICD-10 codes.

Detection of human parechoviruses in stool samples sent to the Robert-Koch-Institute was positively associated with evidence of seizures and/or rash in patients below 4 years of age. This collaboration also lead to a first case report of ADEM following human parechovirus infection.

Conclusion: Digital media help physicians to ask ‘the right questions at the right time’, i.e. when the patient is still accessible. Higher case classification rates could be achieved if physicians were prompted to order pertinent diagnostic procedures in cases of clinical suspicion. The consistent implementation of consensus criteria at the point-of-care may lead to considerable improvements in routine healthcare, clinical research, and surveillance programs at the Robert-Koch-Institute.

1 Introduction

In 2015, U.S. President Barack Obama announced the Precision Medicine Initiative (PMI), urging interdisciplinary biomedical approaches to improve quality of care, especially with regards to overcoming barriers to therapeutic and diagnostic innovation.[1,2] Paving the way to improve the standardization and "meta-analyzability" of clinical data, expert panels have generated a broad spectrum of consensus case definitions, including those for neurologic adverse events such as aseptic meningitis, encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM).[3,4] Although these case definitions are published and readily available, they are hardly ever put to use.[5,6] Clinical presentations of neurologic diseases may range from subtle, inconsistent, or unspecific symptoms to rather obvious clinical presentations, especially in infants and children.[7-11] Unless standardized case criteria are applied, actual case numbers may be underestimated delaying access to timely therapy, detection of disease outbreaks, and safety signals.[9,11,12]

Traditionally, ICD-codes (International Catalog of Diseases) have been used for surveillance programs as they are commonly used for billing purposes.[13] The fact that ICD-codes are not designed for research use however, created significant problems.[5,11,13] For example, ICD-codes do not distinguish between symptoms and diagnosis and may be highly subjective causing considerable inter-rater variability.[14-17] Unless the same standardized case criteria are applied uniformly, there will be significant inconsistency with regards to ICD coding among different assessors and sites.[14] Electronic health records may thus provide a more comprehensive source of information for the detection of adverse events.[5,18] To a certain degree, standardized case criteria and case definition algorithms can be applied to electronic health records. This approach has been shown to provide significant advantage as it may result in consistent criteria for retrospective analyses and meta-analyses. For the case definitions for aseptic meningitis, encephalitis, myelitis, and ADEM this has been demonstrated successfully in a retrospective study at a Swiss Children's Hospital.[5] The main disadvantage of the use of routine medical records is that not all of the pertinent data will necessarily be documented in busy clinical settings.[5,14] Applying standardized case criteria retroactively will therefore lead to indeterminate results in all instances where the data set required for the case algorithm was incomplete.[5]

The work published by Obermeier et al. in in EBioMedicine is taking the use of standardized case definitions into a prospective mode by exploring the use of digital tools at the point-of-care, assisting the physician in 'asking the right questions at the right time'.[19] The purpose of standardized case classification at the point-of-care would be to obtain complete clinical datasets while the patient is still accessible.[5]

To demonstrate the usefulness of standardized case classification in a quality improvement setting, the clinical characteristics were also analyzed in relation to the virological findings in the respective patients at the Robert-Koch-Institute. As mentioned previously, neuroinfectious and neuroinflammatory diseases such as aseptic meningitis, encephalitis, myeltis, and ADEM may be triggered by a variety of factors, including natural infection or, in rare instances, the administration of a drug or vaccine.[3,4,7,8,11,20,21] Among viral pathogens, human parechoviruses are increasingly recognized as potential triggers of neuroinfectious and/or inflammatory disease.[22-24] The aim of the virologic analyses was to improve our understanding of the clinical picture associated with human parechovirus disease.

The overall objectives of the reported research studies can thus be summarized as follows:

1) To evaluate the completeness of clinical datasets obtained by standardized case classification using the VACC-Tool at the point-of-care to ascertain cases of aseptic meningitis, encephalitis, myelitis, and ADEM.

2) To describe the clinical disease presentations associated with human parechovirus infections in a prospective cohort of hospitalized children with suspected infections of the central nervous system (CNS) with special attention to standardized case criteria.

2 Methods

2.1 The Meningitis Surveillance at Charité (MenSCh) Cohort

A quality improvement/quality management (QM) program was developed at the Charité Department of Pediatrics in 2010/11, in collaboration with the National Reference Centre for Poliomyelitis and Enteroviruses at the Robert-Koch-Institute in Berlin.[20] Pediatric inpatients (age 0-18 years) meeting pre-defined criteria for CNS infection/inflammation (≥3 CNS symptoms, OR ≥1 CNS symptom(s) and lumbar puncture, OR physician diagnosis/ request for entry into the QM program) underwent highly standardized neurologic

assessments, conducted by a specifically trained QM team (Meningitis Surveillance at Charité = MenSCh Cohort). Patients with known seizure disorders, CNS lesion/tumor, acute intoxication, head injury within the last 24 hours, or acute diarrhea/dehydration were not eligible for participation in the QM program.[19,25]

In patients with evidence of pain, standardized and age-appropriate assessments were performed in all age groups (Modified Behavioral Pain Scale[26]; Faces, Legs, Activity, Cry and Consolability Pain Assessment[27]; Faces Pain Scale[28]; Numerical Rating Scale[29]; Visual Analog Scale[30]). If pain was present, the location of the pain during the physical exam was investigated in coordination with the primary clinical team.

If available, stool samples were collected and provided to the Robert-Koch-Institute for blinded reverse transcription polymerase chain reaction (RT-PCR) analyses for enteroviruses and human parechoviruses as described previously.[25]

Stool samples were stored at 4°C for a maximum of three days prior to isolation of viral ribonucleic acid (RNA) and sample processing.[31] Detection of human parechovirus RNA was performed using a one-step RT-PCR kit with primers described by Benschop et al.[31,32]

The QM measures did not interfere with routine care in participating patients, but treating physicians were informed of the virologic findings as soon as available.

2.2 Implementation of a digital case classification tool at the point-of-care

The VACC-Tool (Vienna Vaccine Safety Initiative Automated Case Classification Tool) was made available both as a mobile handheld application and as a web-user interface to be used as a standardized patient assessment tool.

The VACC-Tool was developed by the Vienna Vaccine Safety Initiative in an algorithm-based questions-and-answer format following the user-friendly principles of design thinking.[33] Data entered into the VACC-Tool were classified according to the case definitions for meningitis, encephalitis, myelitis, and ADEM as well as the respective levels of diagnostic certainty. Level 1 is designed to be closest to gold standard, with levels 2 and 3 being less stringent but still evident. Level 4 represents a case with insufficient data, whereas level 5 indicates that case criteria are definitely not fulfilled.[3,4]

For comparison, the same clinical cases were re-classified using the same algorithms retrospectively based on data abstracted from routine care electronic health records.

Data entry verification was performed by specifically trained medical staff, in compliance with ICH-Good Clinical Practice. Facilitating bioinformatical, algorithm-based analysis, any undocumented clinical signs or symptoms were reported as 'absent'. Data entered into the VACC-Tool are compliant with regulatory requirements and data standards issued by the Clinical Data Interchange Standards Consortium (CDISC, www.cdisc.org).[34-36]

2.3 Statistics

Statistical analysis was performed using SPSS software. According to U.S. Food and Drug Administration Guidelines for reporting diagnostic test results in the absence of a diagnostic gold standard, overall rates of agreement (ORA) as well as positive percent agreement (PPA) and negative percent agreement (NPA) were determined for comparison of VACC-Tool case classification results with retrospective application of the same case criteria.[37] Cohen's kappa coefficient was calculated to assess the coincidence of concordant/discordant results. P-values less than 0.05 were considered statistically significant. Reported results were calculated with 95% confidence intervals based on the total sample size of 521 with a point estimate of 0.5 corresponding to the point of largest variance within a binomial distribution.[5]

Objective machine learning algorithms were applied to the anonymized dataset to identify key features characterizing meningitis, encephalitis, myelitis, and ADEM if applicable.[19,25,38] The Kullback-Leibler(KL)-divergence was used to quantify levels of relevance of each key feature to the respective case classification (i.e. increasing relevance with increasing numbers).[19,25,39]

2.4 Standard protocol approvals

The QM program was approved by the Charité institutional Review Board (IRB) in Berlin, Germany (EA2/161/11). Informed consent procedures were waived by the IRB for the purpose of quality improvement and infection control. Individual consent for publication was obtained for the ADEM case.

3 Results

3.1 Unbiased syndromic surveillance for aseptic meningitis, encephalitis, myelitis, and ADEM using the VACC-Tool at the point-of-care

From November 2010 to June 2013, 68,921 patients attended the pediatric emergency room at the Charité University Medical Center. Of these, 11,575 patients were hospitalized, with 521 patients (4.5%) consecutively fulfilling the criteria for participation in the QM program; mean age: 7.6 years (0.03;18.03), gender: 51% male. The selection process is displayed in **Figure 1**.

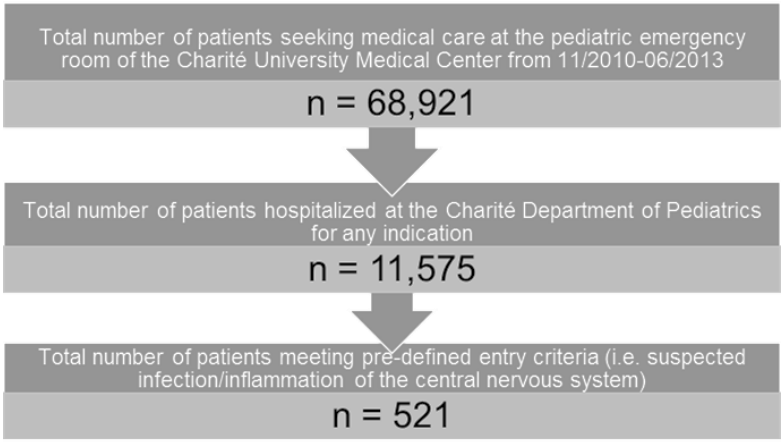

Fig. 1 Case selection process.[19]

Using the VACC-Tool at the point-of-care, 180 cases were classified as either aseptic meningitis, encephalitis, or ADEM. No cases were classified as myelitis. A total of 194 cases were ruled out with certainty and 147 cases remained a “level 4” (= indeterminate) signifying that the information was incomplete for fulfilling the respective algorithm. Of note, the missing data represented laboratory, electrophysiology, or imaging studies that had not been ordered in the context of routine care whereas all clinical datasets were complete.

3.1.1 Key features in patients classified as aseptic meningitis, encephalitis, and ADEM

Independent from the underlying case classification algorithm, KL-distance analysis revealed that pleocytosis in the cerebrospinal fluid (KL 8.34), followed by negative gram stain (KL 4.75) and bacterial culture results (KL 3.38) were critical for the classification of aseptic meningitis.

For ADEM and encephalitis, histological evidence yielded highest KL-values (7.6), which then automatically lead to classifications with highest levels of evidence ('level 1' of diagnostic certainty). Second highest KL-values for ADEM and encephalitis were assigned to clinical signs of cranial nerve deficits (KL 0.88 and 0.68 respectively). The absence of fever was a key feature of ADEM. Unbiased feature selection results confirmed the combination of both, clinical and laboratory/neuroimaging data as 'relevant' (**Table 1**).

Table 1 Feature selection results are displayed for VACC-Tool classifications of aseptic meningitis, encephalitis, and ADEM. Dark grey background color indicates a positive correlation (i.e. the presence of a symptom is important) between clinical sign/laboratory finding and case classification. Light grey background color indicates a negative correlation (i.e. the absence of a symptom is important). Numbers are KL-divergences, indicating increasing importance with increasing number. [19]

	Bulging fontanelle	Reduced level of consciousness	Lethargy	Cranial nerve deficit	Fever (body temperature ≥38.0°C)	Sensory abnormalities	Cerebellar deficits (e.g. dysmetria)	Focal cortical signs (e.g. alexia)	Decreased deep tendon reflexes	Behavioral changes	Pleocytosis in cerebrospinal fluid	Gram stain	Neuroimaging
Aseptic Meningitis	0.05	0.12	0.28	0.88			1.32				8.34	4.7	
Encephalitis				0.68		0.26	0.06	0.13			0.19		
ADEM				0.88	0.54	0.29		0.04	0.05	0.32			0.77

3.1.2 Comparison between retrospective case classification and prospective case classification using the VACC-Tool

When applying the same case algorithms to the routine medical records of the 521 patients retrospectively, 33 cases (6.4%) were missed and 38 cases (7.3%) misclassified. In contrast to use of the VACC-Tool at the point-of-care, pertinent clinical data were not available in the health records of 33 patients. The discrepancy between prospective and retrospective case classification results, were highest for complex disease entities such as encephalitis and ADEM in particular. Cohen's kappa coefficients for assessing coincidence of concordant/discordant results were almost perfect for aseptic meningitis, whereas they were considerably lower for encephalitis and ADEM (**Table 2**).

Table 2 Comparison of VACC-Tool case classification at the point of care (VACC) with retrospective case classification (RETRO) based on the same algorithms with overall rates of agreement (ORA), positive percent agreement (PPA), negative percent agreement (NPA), and kappa scores (k) (n = 521). [19]

Categories	Aseptic meningitis	Encephalitis	ADEM
VACC+	63	65	76
VACC−	458	456	445
RETRO+	61	65	69
RETRO−	460	456	452
VACC+/RETRO+	59	40	54
VACC+/RETRO−	4	25	22
VACC−/RETRO+	2	25	15
VACC−/RETRO−	456	431	430
ORA [95% CI]	99% [95; 100]	90% [86; 94]	93% [89; 97]
PPA [95% CI]	97% [93; 100]	62% [58; 66]	78% [74; 82]
NPA [95% CI]	99% [95; 100]	95% [91; 99]	95% [91; 99]
K	0.95***	0.56***	0.70***

*** $p < 0.001$.

3.1.3 Comparison between ICD-10 codes and prospective case classification using the VACC-Tool

Review of ICD-codes among the same 521 cases revealed that 116 cases (22.3%) would have been missed. The most commonly missed diagnosis was ADEM (76.7%). Additional 38 cases would have been misclassified (e.g. encephalitis falsely as aseptic meningitis).

3.2 Key clinical features in parechovirus positive patients

From October 2010 to December 2012, stool samples were collected prospectively, if available. A total of 284 samples were collected, 12 (4.2%) tested positive for human parechoviruses. In two cases, human parechovirus and enterovirus were detected simultaneously but no alternative viral or bacterial pathogens were detected during the routine work-up. Patients infected with human parechoviruses were significantly younger in comparison to those negative for human parechoviruses (mean age, 1.1 vs. 7.09 years; p <0.001). Notably, all 12 patients testing positive for human parechoviruses from October 2010 to December 2012 were below four years of age.

Based on standardized QM (VACC-Tool) assessments, seizures, rash, change of personality, irritability, lethargy, sensitivity to touch, and vomiting were detected most commonly among parechovirus positive patients. Other neurologic symptoms observed occasionally in these patients (≤ 2 cases) included jumpiness, phono- and photophobia, altered level of consciousness, and nystagmus. Objective bioinformatics analysis of QM

data using machine learning algorithms confirmed the absence of headaches as a key feature in patients testing positive for human parechoviruses (KL 4.21; p <0.0005). Additional key features were (in descending order) the absence of cranial nerve deficits (KL 1.48), reduced respiratory drive/apnea (KL 0.609), focal cortical signs (KL 0.353), amnesia (KL 0.281), hallucinations (KL 0.211), and signs of meningeal irritation (KL 0.129), in addition to the presence of seizures (KL 0.104).

3.3 Using the VACC-Tool to facilitate individualized medicine – a case of ADEM following human parechovirus infection

During continuation of the QM program in 2013, a first stool sample was tested positive in a previously healthy 5-year-old female presenting with acute left-sided flaccid hemiparesis and fatigue preceded by a febrile respiratory illness approximately two weeks prior. The patient had not received any immunization for three years.

During almost three years of QM surveillance, this was the only patient presenting with evidence of human parechovirus infection above the age of four years. Using the VACC-Tool, this patient was also classified as fulfilling ADEM case criteria at the highest level of diagnostic certainty. Standardized clinical assessments using the VACC-Tool confirmed left-sided hemiparesis and revealed hyposensitivity, hyporeflexia, and left-sided central facial nerve palsy corresponding to a contralateral white matter injury. Cranial computed tomography and magnetic resonance imaging were considered highly consistent with ADEM by independent neuro-radiological assessment on hospital day one (**Figure 2**).

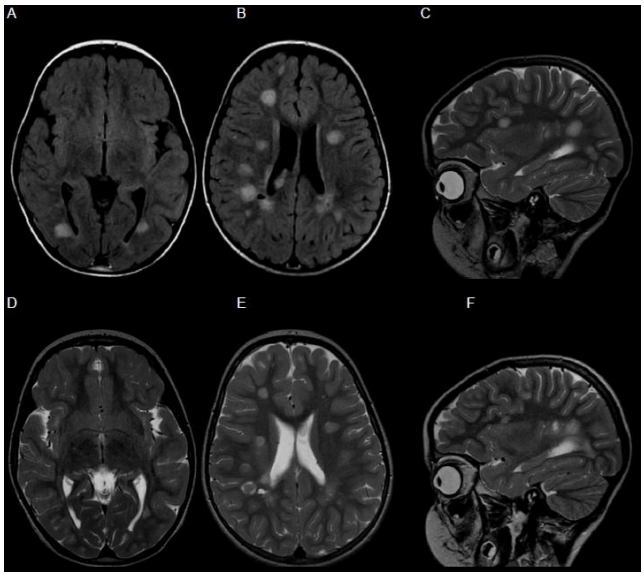

Fig. 2 Initial (A-C) and follow-up (D-F) magnetic resonance imaging (MRI) with axial (A, B, D, E) and sagittal planes (C, F): MRI on hospital day one shows disseminated supratentorial hyperintense white matter lesions predominant on the right side (A, B, T2-weighted FLAIR). Occipital lesions, present on both sides, show maximum diameters of 21mm (C, T2 frFSE). Follow-up MRI after five months shows very slight regredience of demyelination foci (D-F, T2 frFSE).

Initial analysis of the cerebrospinal fluid (CSF) on hospital day two revealed mild pleocytosis (7 leukocytes/µl, 98% lymphocytes) with evidence of intrathecal IgM synthesis. CSF cultures for mycobacteria, light microscopy for bacteria and fungi, serologies for borrelia, mycoplasma, toxoplasma, *Taenia solium*, for herpes simplex (HSV), varicella-zoster, Epstein-Barr, mumps, measles, and rubella viruses, as well as PCR for herpes simplex, varicella-zoster, Epstein-Barr, measles, mumps, and rubella viruses were all negative. Empirical acyclovir therapy was stopped on day three of hospitalization for negative HSV-PCR results. A brain biopsy obtained three months after the initial presentation due to persisting neuroimaging abnormalities supported the diagnosis of ADEM histologically with marked perivascular CD3- and CD8-positive lympho-monocytic infiltration and patchy areas of demyelination. On hospital day three, intravenous pulse methylprednisolone therapy was initiated for five days (25 mg/kg/day), followed by oral prednisolone for 13 weeks total (starting with 1.5 mg/kg/day). Within four days, the central facial nerve palsy improved considerably. The hemiparesis improved over the following four months whereas MRI findings consistent with ADEM persisted for more than five months.

4 Discussion

We report the successful implementation of a QM program for the standardized clinical and virologic surveillance of aseptic meningitis, encephalitis, myelitis, and ADEM at the point-of-care. The use of digital tools at the point-of-care contributed significantly to enhanced data quality and consistency. With syndromic surveillance linked to virologic analyses at the Robert-Koch-Institute, we were able to identify specific disease features that may be associated with human parechovirus infections in children. The digital tool that was tested in this QM program may be useful in a variety of settings, as exemplified below.

Syndromic surveillance of rare diseases and adverse events following immunization

One of the key challenges in syndromic surveillance is the inconsistency of data captured in routine care.[5,13,17] With the help of digital case algorithms, standardized case ascertainments have become feasible opening new opportunities for precision medicine and syndromic surveillance programs.[5,19]

In the past, clinical studies and surveillance programs have largely relied on ICD-codes for the identification of cases.[16] It is widely known however, that the value of ICD coding for clinical research may be limited significantly by inter-rater variability and ascertainment bias.[11,13,16,17] Standardized case criteria on the other hand, will harmonize and streamline case classification across sites, but only if all pertinent data are available in the medical records.[5] In some instances, the result will remain 'indeterminate' if certain parameters have either not been assessed or not documented during routine care.[5] According to the U.S. Centers for Disease Control and Prevention Guidelines for Evaluating Surveillance Systems, the quality of any surveillance systems depends on 'completeness' of data[40], i.e. capturing 100% of pertinent positive as well as pertinent negative data. In clinical practice however, this is rarely the case. For example, if no reference can be found to "headache" in a patient's hospital record, it will be impossible to determine if headaches were absent or if the topic had not been raised or documented.

The VACC-Tool was specifically designed to prompt physicians to obtain all relevant clinical information (as required for any of the four case definitions) immediately, at the point-of-care. Further detail was requested if a superior question had been affirmed. Thus, the VACC-Tool was made to fit the clinician work flow while improving data granularity at the same time. Consistent use of the VACC-Tool facilitates the consistent monitoring for rare diseases.[31] As all patients are undergoing the same assessments during the entire surveillance period, the denominator will be known as well. This has immediate impact on the surveillance of adverse events following immunization, which are known to be rare but of clinical importance once they occur.[41,42] ADEM, a known rare but serious adverse event following immunization for example, is known to be underreported.[43,44] For regulatory agencies in charge of vaccine safety monitoring, such as the Paul Ehrlich Institute in Germany, it will be important to be able to communicate incidence rates to the general public. Secondly, it will be important to communicate the risk of adverse events following

immunization in relation to the risk of experiencing the same adverse event triggered by infectious and other “natural” triggers.[42]

Bioinformatics and down-stream applications resulting in new diagnostic insight

By capturing complete clinical datasets, the VACC-Tool provides highly granular datasets allowing bioinformaticians to perform unbiased machine learning algorithms such as feature selection and mathematical decision models.[19] This may lead to the development of evidence-based clinical prediction models and provide new diagnostic insight.[19,31] In the long term, if standardized datasets are obtained across multiple sites and observation periods, diagnostic algorithms will be refined and improved further using the feedback from “real-world” clinical data. Eventually, pattern recognition and feature selection algorithms may be utilized to assist the clinician in their daily work, by alerting them to specific diagnostic tests that might be required to “rule-in” or “rule-out” a specific diagnosis with certainty.[19] Digital tools and bioinformatics analyses may also help the clinician to identify diagnostic features that were previously overlooked, such as the *absence* of certain symptoms that may make a specific diagnosis more likely, such as the absence of headaches in the case of parechovirus infections or the absence of fever as a key feature of ADEM.[19,25] Digital algorithms, when used in conjunction with large datasets, may also help to clarify questions that have not yet been settled by experts. For example, fever was not a criterion for or against ADEM in the underlying case definition used in this QM project.[3] The incidence of fever in ADEM however, has been the subject of debate, as some authors postulate the presence of fever as a distinctive feature discriminating monophasic ADEM from multiple sclerosis in children, whereas others consistently dispute this observation.[3,45] It will be important to develop and enhance case definitions towards higher diagnostic accuracy and precision medicine.

Linkage between virologic and clinical outcomes

Parechovirus surveillance has been implemented as part of polio- and enterovirus surveillance not only by the Robert-Koch-Institute, but also in several other countries in Europe and North America.[46,47] This is leading to an increasing knowledge base regarding the prevalence and incidence of infectious diseases in the general population, but clinical

data provided in the context of sentinel surveillance programs may be sparse. This represents a missed opportunity to studying the burden of infectious diseases in specific at-risk populations as well as to educate clinicians what to look at clinically when suspecting a case. With the help of standardized clinical assessments, we were able to detect a potential link between human parechovirus infection, seizures, and rash in infants and toddlers.[25] As mentioned above, the *absence* of headaches and other neurologic complications seem to be suggestive of human parechovirus infection.[25]
In line with common assumptions on at-risk groups, our analysis confirmed highest rates of parechovirus infections in infants and toddlers.[22]

Alerting the clinician to rare diseases and potential causes

Standardized case classification is not only helpful to investigate the overall prevalence of infectious diseases and symptoms that are commonly associated with them, but also to delineate rare and unusual presentations in real-time.[11,31] In the case of this QM program, we were able to identify, and to describe in detail, a first case of ADEM after parechovirus infection.[31] Furthermore, we were able to show that this case represented an “outlier” with respect to age compared to the remaining patients with parechovirus infections.[25] This will provide useful insight to neuro-immunologist researching the biological link between acute viral infections and delayed autoimmune diseases following several weeks thereafter.[48]
The clinical findings in this case are in line with reports of a potential link between other *picornaviridae* and neuroinflammatory disease.[49,50] These findings further highlight the need to rule out certain infections when encountering a case of ADEM, before suspecting other potential triggers such as vaccines and certain medications.[31]

Limitations and future perspectives

The present proof-of-concept study assessing the impact of standardized case classification at the point-of-care was limited by the validation setting in which it was conducted.[19] The QM program refined the analysis to one single site as well as to a system where the case ascertainments were done by a different (QM) team compared to routine clinical care. This was intentional to allow the independent validation of a QM measure compared to routine care, but it also implied that physicians were blinded to the case

classification results obtained by the QM team. Future versions and updates for use of the VACC-Tool in routine care may incorporate additional features such as digital alerts reminding the clinician to consider specific laboratory, electrophysiology, or neuroimaging studies if the clinical criteria would otherwise be fulfilled.[19,51] Future use of the VACC-Tool would also include additional, related diagnostic algorithms and further validation studies within the routine work flow.[51] The main limitation of the present Version 1.0 of the VACC-Tool lies in the potential for effect modifications in favor of the case definitions represented therein, (i.e. aseptic meningitis, encephalitis, or ADEM). With an increasing number of case definition algorithms, the balanced and comprehensive differential diagnosis of multiple potential adverse events will be facilitated. The complexity of automated algorithm-based case classification will likely increase further with increasing numbers of case algorithms, thereby providing additional assistance to clinicians working in a busy clinic or emergency room setting.

Medical research and innovation projects such as the U.S. Precision Medicine Initiative (PMI) are geared towards the early detection of safety signals as well as the accurate diagnosis and pro-active prevention of diseases.[1,2] The VACC-Tool was designed in full compliance with CDISC standards for interoperability and meta-analyzability of data across different sites.[35] VACC-Tool algorithms could be integrated into routine care electronic health records for the automated submission of safety signals or adverse events following immunization/drug administration to regulatory agencies.[6,18,52] Importantly, not only the occurrence of adverse events could be tracked by using the VACC-Tool, but also the *absence* of adverse events, which will ultimately be required as proof of evidence for the safety and tolerability of medicinal products and biologics. To carry the precision medicine paradigm further, digital case ascertainments may also be useful to support the identification of predictive laboratory biomarkers thereby helping to overcome barriers to therapeutic innovation as outlined in a commentary by M. Twilt published in EBioMedicine in 2016.[51]

Finally, empowering patients who are willing to participate in collaborating with healthcare professionals is another aspect of precision medicine.[1,2] If adopted to lay language, digital tools may also contribute to strengthen the monitoring of patient reported outcomes and

the pro-active monitoring vaccine safety and effectiveness, adding another angle to traditional surveillance methodologies.

Conclusion

Using an innovative mobile application for the unbiased and timely detection of aseptic meningitis, encephalitis, myelitis, and ADEM enabled physicians to 'ask the right questions at the right time', thereby gathering a complete dataset of positive as well as pertinent negative data for algorithm-based case classifications. Standardized syndromic surveillance will help to avoid misinterpretation and underestimation of actual case numbers, thus facilitating the timely access to therapy and the timely transmission of comprehensive safety signals. Comprehensive and standardized clinical assessments are a prerequisite for the *de novo* identification of potential triggers or unique sets of signs and symptoms that may be useful as a "tip-off" for the clinician to consider a certain diagnosis. Additional research will be needed to improve diagnostic algorithms further and to inform stakeholders about the feasibility and generalizability of this approach.

5 References

1. Duffy DJ. Problems, challenges and promises: perspectives on precision medicine. *Briefings in bioinformatics* 2015.
2. The White House. FACT SHEET: President Obama's Precision Medicine Initiative. 2015. https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative (accessed 18th of February 2016.
3. Sejvar JJ, Kohl KS, Bilynsky R, et al. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2007; **25**(31): 5771-92.
4. Tapiainen T, Prevots R, Izurieta HS, et al. Aseptic meningitis: case definition and guidelines for collection, analysis and presentation of immunization safety data. *Vaccine* 2007; **25**(31): 5793-802.
5. Rath B, Magnus M, Heininger U. Evaluating the Brighton Collaboration case definitions, aseptic meningitis, encephalitis, myelitis, and acute disseminated encephalomyelitis, by systematic analysis of 255 clinical cases. *Vaccine* 2010; **28**(19): 3488-95.
6. Muehlhans S, Richard G, Ali M, et al. Safety reporting in developing country vaccine clinical trials-a systematic review. *Vaccine* 2012; **30**(22): 3255-65.
7. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* 2010; **10**(12): 835-44.
8. Kelly TA, O'Lorcain P, Moran J, et al. Underreporting of viral encephalitis and viral meningitis, Ireland, 2005-2008. *Emerg Infect Dis* 2013; **19**(9): 1428-36.
9. Koelman DL, Mateen FJ. Acute disseminated encephalomyelitis: current controversies in diagnosis and outcome. *J Neurol* 2015.

10. Curtis S, Stobart K, Vandermeer B, Simel DL, Klassen T. Clinical features suggestive of meningitis in children: a systematic review of prospective data. *Pediatrics* 2010; **126**(5): 952-60.
11. Britton PN, Dale RC, Elliott E, et al. Pilot surveillance for childhood encephalitis in Australia using the Paediatric Active Enhanced Disease Surveillance (PAEDS) network. *Epidemiology and infection* 2016: 1-11.
12. Hughes PS, Jackson AC. Delays in initiation of acyclovir therapy in herpes simplex encephalitis. *The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques* 2012; **39**(5): 644-8.
13. O'Malley KJ, Cook KF, Price MD, Wildes KR, Hurdle JF, Ashton CM. Measuring diagnoses: ICD code accuracy. *Health services research* 2005; **40**(5 Pt 2): 1620-39.
14. Horwitz RI, Yu EC. Assessing the reliability of epidemiologic data obtained from medical records. *J Chronic Dis* 1984; **37**(11): 825-31.
15. Gundlapalli AV, Tang H, Tonnierre C, et al. Validity of electronic medical record-based rules for the early detection of meningitis and encephalitis. *AMIA Annu Symp Proc* 2007: 299-303.
16. St Germaine-Smith C, Metcalfe A, Pringsheim T, et al. Recommendations for optimal ICD codes to study neurologic conditions: a systematic review. *Neurology* 2012; **79**(10): 1049-55.
17. Bellis JR, Kirkham JJ, Nunn AJ, Pirmohamed M. Clinical coding of prospectively identified paediatric adverse drug reactions--a retrospective review of patient records. *BMC pharmacology & toxicology* 2014; **15**: 72.
18. Linder JA, Haas JS, Iyer A, et al. Secondary use of electronic health record data: spontaneous triggered adverse drug event reporting. *Pharmacoepidemiol Drug Saf* 2010; **19**(12): 1211-5.
19. Obermeier P, Muehlhans S, Hoppe C, et al. Enabling Precision Medicine With Digital Case Classification at the Point-of-Care. 2016. http://dx.doi.org/10.1016/j.ebiom.2016.01.008.
20. Hayasaka D, editor. Pathogenesis of Encephalitis: INTECH; 2011.
21. Nakayama T, Onoda K. Vaccine adverse events reported in post-marketing study of the Kitasato Institute from 1994 to 2004. *Vaccine* 2007; **25**(3): 570-6.
22. Renaud C, Harrison CJ. Human Parechovirus 3: The Most Common Viral Cause of Meningoencephalitis in Young Infants. *Infectious disease clinics of North America* 2015; **29**(3): 415-28.
23. Rotbart HA. Enteroviral infections of the central nervous system. *Clin Infect Dis* 1995; **20**(4): 971-81.
24. Saitoh A, Sawyer MH, Leake JA. Acute disseminated encephalomyelitis associated with enteroviral infection. *Pediatr Infect Dis J* 2004; **23**(12): 1174-5.
25. Karsch K, Obermeier P, Seeber L, et al. Human Parechovirus Infections Associated with Seizures and Rash in Infants and Toddlers. *Pediatr Infect Dis J* 2015.
26. Taddio A, Nulman I, Koren BS, Stevens B, Koren G. A revised measure of acute pain in infants. *Journal of pain and symptom management* 1995; **10**(6): 456-63.
27. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: a behavioral scale for scoring postoperative pain in young children. *Pediatric nursing* 1997; **23**(3): 293-7.
28. Bieri D, Reeve RA, Champion GD, Addicoat L, Ziegler JB. The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: development, initial validation, and preliminary investigation for ratio scale properties. *Pain* 1990; **41**(2): 139-50.
29. Miro J, Castarlenas E, Huguet A. Evidence for the use of a numerical rating scale to assess the intensity of pediatric pain. *European journal of pain* 2009; **13**(10): 1089-95.
30. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? *Pain* 1997; **72**(1-2): 95-7.
31. Obermeier PE, Karsch K, Hoppe C, et al. Acute Disseminated Encephalomyelitis After Human Parechovirus Infection. *The Pediatric infectious disease journal* 2016; **35**(1): 35-8.
32. Benschop K, Molenkamp R, van der Ham A, Wolthers K, Beld M. Rapid detection of human parechoviruses in clinical samples by real-time PCR. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology* 2008; **41**(2): 69-74.

33. Seeber L, Michl B, Rundblad G, et al. A design thinking approach to effective vaccine safety communication. *Current drug safety* 2015; **10**(1): 31-40.
34. Daniel C, Erturkmen GB, Sinaci AA, Delaney BC, Curcin V, Bain L. Standard-based integration profiles for clinical research and patient safety. *AMIA Jt Summits Transl Sci Proc* 2013; **2013**: 47-9.
35. Leroux H, Lefort L. Semantic enrichment of longitudinal clinical study data using the CDISC standards and the semantic statistics vocabularies. *J Biomed Semantics* 2015; **6**: 16.
36. Souza T, Kush R, Evans JP. Global clinical data interchange standards are here! *Drug Discov Today* 2007; **12**(3-4): 174-81.
37. U.S. Food and Drug Administration. Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests. 2007. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm (accessed 18th of February 2016.
38. Hall MA. Correlation-Based Feature Subset Selection for Machine Learning. Hamilton, New Zealand: University of Waikato; 1998.
39. Kullback S. Letter to the Editor: The Kullback-Leibler Distance. *The American Statistician* 1987; **41**(4): 340-1.
40. Klaucke D, Buehler J, Thacker S, Parrish R, Trowbridge F, R B. Guidelines for Evaluating Surveillance Systems. 1988. http://www.cdc.gov/mmwr/preview/mmwrhtml/00001769.htm (accessed 18th of February 2016.
41. Miller E, Haber P, Hibbs B, Broder K. Surveillance for Adverse Events Following Immunization Using the Vaccine Adverse Event Reporting System (VAERS). 2014. http://www.cdc.gov/vaccines/pubs/surv-manual/chpt21-surv-adverse-events.html#f5.
42. Chen RT, Rastogi SC, Mullen JR, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994; **12**(6): 542-50.
43. Pellegrino P, Carnovale C, Perrone V, et al. Acute disseminated encephalomyelitis onset: evaluation based on vaccine adverse events reporting systems. *PloS one* 2013; **8**(10): e77766.
44. Moris G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis revisited. *JAMA internal medicine* 2014; **174**(9): 1511-2.
45. Dale RC, Branson JA. Acute disseminated encephalomyelitis or multiple sclerosis: can the initial presentation help in establishing a correct diagnosis? *Arch Dis Child* 2005; **90**(6): 636-9.
46. Abedi GR, Watson JT, Pham H, Nix WA, Oberste MS, Gerber SI. Enterovirus and Human Parechovirus Surveillance - United States, 2009-2013. *MMWR Morbidity and mortality weekly report* 2015; **64**(34): 940-3.
47. van der Sanden SM, Koopmans MP, van der Avoort HG. Detection of human enteroviruses and parechoviruses as part of the national enterovirus surveillance in the Netherlands, 1996-2011. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* 2013; **32**(12): 1525-31.
48. Wender M. Acute disseminated encephalomyelitis (ADEM). *Journal of neuroimmunology* 2011; **231**(1-2): 92-9.
49. Wong KT. Emerging and re-emerging epidemic encephalitis: a tale of two viruses. *Neuropathology and applied neurobiology* 2000; **26**(4): 313-8.
50. Sin J, Mangale V, Thienphrapa W, Gottlieb RA, Feuer R. Recent progress in understanding coxsackievirus replication, dissemination, and pathogenesis. *Virology* 2015; **484**: 288-304.
51. Twilt M. Precision Medicine: The new era in medicine. 2016. http://dx.doi.org/10.1016/j.ebiom.2016.02.009.
52. Dal Pan GJ. Commentary on "Secondary use of electronic health record data: spontaneous triggered adverse drug event reporting" by Linder et al. *Pharmacoepidemiol Drug Saf* 2010; **19**(12): 1216-7.

Affidavit

I, Patrick Obermeier, certify under penalty of perjury by my own signature that I have submitted the thesis on the topic “Automated case classification of neurologic adverse events at the point-of-care and enhanced virologic surveillance – new avenues towards quality improvement and precision medicine”. I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The section on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) corresponds to the URM (s. o.) and are answered by me. My contribution in the selected publication for this dissertation corresponds to those that are specified in the following joint declaration with the responsible person and supervisor.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

_____ _____

Date Signature

Declaration of Contributions

Patrick Obermeier made the following contributions to the publications listed below:

Publication 1: **Obermeier P**, Muehlhans S, Hoppe C, Karsch K, Tief F, Seeber L, Chen X, Conrad T, Boettcher S, Diedrich S, Rath B. Enabling Precision Medicine with Digital Case Classification at the Point-of-Care. EBioMedicine 2016. Impact Factor: N/A

Contribution in detail: Major contribution to data acquisition. Primary analysis and interpretation of data, Writing the initial draft manuscript as well as revised manuscripts during the peer review process. Data management, data quality checks and quality assurance, basic statistical analysis (under supervision).

Publication 2: Karsch K, **Obermeier P**, Seeber L, Chen X, Tief F, Mühlhans S, Hoppe C, Conrad T, Böttcher S, Diedrich S, Rath B. Human Parechovirus Infections Associated with Seizures and Rash in Infants and Toddlers. Pediatr Infect Dis J. 2015. Impact Factor 2014/15: 2.723

Contribution in detail: Contributed (as part of a team) to data acquisition, data entry and the writing of the manuscript. Contribution to revisions of the manuscript. Approval of the final version.

Publication 3: **Obermeier PE**, Karsch K, Hoppe C, Seeber L, Schneider J, Mühlhans S, Chen X, Tief F, Kaindl AM, Weschke B, Böttcher S, Diedrich S, Rath B. Acute Disseminated Encephalomyelitis After Human Parechovirus Infection. Pediatr Infect Dis J. 2016. Impact Factor 2014/15: 2.723

Contribution in detail: Acquisition, analysis and interpretation of data, drafting of the manuscript. Data management, data quality check and quality assurance, statistical analysis.

Signature, date and stamp of the thesis supervisor

_____

Signature of the doctoral candidate

_____

Enabling Precision Medicine with Digital Case Classification at the Point-of-Care

Obermeier P et al., 2016

http://dx.doi.org/10.1016/j.ebiom.2016.01.008

http://dx.doi.org/10.1016/j.ebiom.2016.01.008

http://dx.doi.org/10.1016/j.ebiom.2016.01.008

http://dx.doi.org/10.1016/j.ebiom.2016.01.008

http://dx.doi.org/10.1016/j.ebiom.2016.01.008

http://dx.doi.org/10.1016/j.ebiom.2016.01.008

Precision Medicine: The new era in medicine.

Twilt M, 2016

http://dx.doi.org/10.1016/j.ebiom.2016.02.009

http://dx.doi.org/10.1016/j.ebiom.2016.02.009

Human Parechovirus Infections Associated with Seizures and Rash in Infants and Toddlers

Karsch K et al., 2015

http://dx.doi.org/10.1097/INF.0000000000000802

http://dx.doi.org/10.1097/INF.0000000000000802

http://dx.doi.org/10.1097/INF.0000000000000802

http://dx.doi.org/10.1097/INF.0000000000000802

http://dx.doi.org/10.1097/INF.0000000000000802

http://dx.doi.org/10.1097/INF.0000000000000802

http://dx.doi.org/10.1097/INF.0000000000000802

Acute Disseminated Encephalomyelitis After Human Parechovirus Infection

Obermeier PE et al., 2016

http://dx.doi.org/10.1097/INF.0000000000000928

http://dx.doi.org/10.1097/INF.0000000000000928

http://dx.doi.org/10.1097/INF.0000000000000928

http://dx.doi.org/10.1097/INF.0000000000000928

Curriculum Vitae

For reasons of data protection, the Curriculum Vitae is not published in the online version.

For reasons of data protection, the Curriculum Vitae is not published in the online version.

Publications and Presentations

Publications

Rath B, Conrad T, Myles P, Alchikh M, Ma X, Hoppe C, Tief F, Chen X, **Obermeier P**, Kisler B, Schweiger B*. Influenza and other Respiratory Viruses: Standardizing Disease Severity in Surveillance and Clinical Trials*. Expert Rev Anti Infect Ther. 2017 Jun;15(6):545-568. doi: 10.1080/14787210.2017.1295847. Epub 2017 May 12.

Böttcher S, **Obermeier PE**, Diedrich S, Kaboré Y, D´Alfonso R, Pfister H, Kaiser R, Di Cristanziano V. *Genome Sequence of a Novel Human Parechovirus Type 17*. Genome Announc. 2017 Feb 23;5(8). pii: e01649-16. doi: 10.1128/genomeA.01649-16.

Rath B, Chen X, Spies V, Muehlhans S, **Obermeier P**, Tief F, Seeber L, Karsch K, Milde J, Skopnik H, Schweiger B, Duwe SC. *Prospective surveillance of antiviral resistance in hospitalized infants less than 12 months of age with A(H3N2) influenza infection and treated with oseltamivir*. Antivir Ther. 2017 Feb 16. doi: 10.3851/IMP3141. [Epub ahead of print].

Seeber L, Conrad T, Hoppe C, **Obermeier P**, Chen X, Karsch K, Muehlhans S, Tief F, Boettcher S, Diedrich S, Schweiger B, Rath B. *Educating parents about the vaccination status of their children: A user-centered mobile application*. Prev Med Rep. 2017 Jan 14;5:241-250. doi: 10.1016/j.pmedr.2017.01.002. eCollection 2017 Mar.

Holt D, Bouder F, Elemuwa C, Gaedicke G, Khamesipour A, Kisler B, Kochhar S, Kutalek R, Maurer W, **Obermeier P**, Seeber L, Trusko B, Gould S, Rath B. *The importance of the patient voice in vaccination and vaccine safety—are we listening?* Clin Microbiol Infect. 2016 Dec 1;22 Suppl 5:S146-S153. doi: 10.1016/j.cmi.2016.09.027. Epub 2016 Dec 6.

Hoppe C#, **Obermeier P#**, Muehlhans S, Alchikh M, Seeber L, Tief F, Karsch K, Chen X, Boettcher S, Diedrich S, Conrad T, Kisler B, Rath B. *Innovative Digital Tools and Surveillance Systems for the Timely Detection of Adverse Events at the Point of Care: A*

Proof-of-Concept Study. Drug Saf. 2016 Oct;39(10):977-88. doi: 10.1007/s40264-016-0437-6.

- Comment in Reactions Weekly (2016): Mobile tools to detect AEs successfully used in Germany. Reactions Weekly (2016) 1609: 9. doi:10.1007/s40278-016-19305-5.

Böttcher S, **Obermeier PE**, Neubauer K, Diedrich S; Laboratory Network for Enterovirus Diagnostics. *Recombinant Enterovirus A71 Subgenogroup C1 Strains, Germany, 2015*. Emerg Infect Dis. 2016 Oct;22(10):1843-6. doi: 10.3201/eid2210.160357.

Karsch K, Chen X, Miera O, Peters B, **Obermeier P**, Francis RC, Amann V, Duwe S, Fraaij P, Heider A, de Zwart M, Berger F, Osterhaus A, Schweiger B, Rath B. *Pharmacokinetics of Oral and Intravenous Oseltamivir Treatment of Severe Influenza B Virus Infection Requiring Organ Replacement Therapy*. Eur J Drug Metab Pharmacokinet. 2016 Mar 19 [Epub ahead of print].

Obermeier P, Muehlhans S, Hoppe C, Karsch K, Tief F, Seeber L, Chen X, Conrad T, Boettcher S, Diedrich S, Rath B. *Enabling Precision Medicine With Digital Case Classification at the Point-of-Care*. EBioMedicine 2016, http://dx.doi.org/10.1016/j.ebiom.2016.01.008.

- Comment in EBioMedicine (2016): Twilt M. *Precision Medicine: The new era in medicine.* EBioMedicine (2016), http://dx.doi.org/10.1016/j.ebiom.2016.02.009

Obermeier PE, Karsch K, Hoppe C, Seeber L, Schneider J, Mühlhans S, Chen X, Tief F, Kaindl AM, Weschke B, Böttcher S, Diedrich S, Rath B. *Acute Disseminated Encephalomyelitis After Human Parechovirus Infection.* Pediatr Infect Dis J. 2016 Jan;35(1):35-8.

Tief F, Hoppe C, Seeber L, **Obermeier P**, Chen X, Karsch K, Mühlhans S, Adamou E, Conrad T, Beresniak A, Schweiger B, Adam T, Rath B. *An inception cohort study*

assessing the role of pneumococcal and other bacterial pathogens in children with influenza and ILI and a clinical decision model for stringent antibiotic use. Antivir Ther. 2016 Feb 11. doi: 10.3851/IMP3034. [Epub ahead of print].

Karsch K, **Obermeier P**, Seeber L, Chen X, Tief F, Muehlhans S, Hoppe C, Conrad T, Böttcher S, Diedrich S, Rath B. *Human Parechovirus Infections Associated with Seizures and Rash in Infants and Toddlers.* Pediatr Infect Dis J. 2015;34(10):1049-55.

Tuttle R, Weick A, Schwarz WS, Chen X, **Obermeier P**, Seeber L, Tief F, Muehlhans S, Karsch K, Peiser C, Duwe S, Schweiger B, Rath B. *Evaluation of novel second-generation RSV and influenza rapid tests at the point of care.* Diagn Microbiol Infect Dis. 2015;81(3):171-6.

Kundi M, **Obermeier P**, Helfert S, Oubari H, Fitzinger S, Yun JA, Brix M, Rath B. *The impact of the parent-physician relationship on parental vaccine safety perceptions*. Curr Drug Saf. 2015;10(1):16-22.

Chen X, Pouran Yousef K, Duwe S, Karsch K, Grover S, Wahlisch S, **Obermeier P**, Tief F, Muehlhans S, Seeber L, von Kleist M, Schweiger B, Rath B. *Quantitative influenza follow-up testing (QIFT)--a novel biomarker for the monitoring of disease activity at the point-of-care.* PloS One. 2014;9(3):e92500.

Rath B, Tief F, Karsch K, Muehlhans S, **Obermeier P**, Adamou E, Chen X, Seeber L, Peiser C, Hoppe C, von Kleist M, Conrad T, Schweiger B. *Towards a personalised approach to managing influenza infections in infants and children - food for thought and a note on oseltamivir.* Infect Disord Drug Targets. 2013;13(1):25-33.

Rath B, Tief F, **Obermeier P**, Tuerk E, Karsch K, Muehlhans S, Adamou E, Duwe S, Schweiger B. *Early detection of influenza A and B infection in infants and children using conventional and fluorescence-based rapid testing.* J Clin Virol. 2012;55(4):329-33.

Presentations

Obermeier PE, Heim A, Biere B, Hage E, Alchikh M, Conrad T, Schweiger B, Rath B. *HAdV-80: A Novel Adenovirus Causing ARDS and Disseminated Infection with Fatal Outcome*. Oral Presentation, 5th isirv-AVG Conference, Shanghai, China, June 14-16, 2017.

Obermeier P, Di Cristanziano V, Kaiser R, Michel D, Diedrich S, Böttcher S. *Eine one-step RT-PCR zur Amplifikation von HPeV-Vollgenomen [A one-step RT-PCR for full-genome amplification of human parechoviruses]*. Oral Presentation, 9th Clinical Virology Workshop of the Gesellschaft für Virologie [German Society for Virology], Würzburg, Germany, November 4-5, 2016.

Obermeier P, Karsch K, Hoppe C, Seeber L, Schneider J, Muehlhans S, Chen X, Tief F, Kaindl AM, Weschke B, Böttcher S, Diedrich S, Rath B. *Acute Disseminated Encephalomyelitis (ADEM) Following Human Parechovirus Infection –Syndromic Surveillance of Pediatric CNS Infections in Berlin, Germany*. Poster Presentation, 31st Annual Clinical Virology Symposium, Daytona, FL, USA, April 26-29, 2015.

Obermeier P, Hoppe C, Muehlhans S, Karsch K, Tief F, Seeber L, Chen X, Rath B. Meningitis, Encephalitis, Myelitis and ADEM in Children: *Automated Case Ascertainment (ChAT Analysis) in Real-Time*. Oral Presentation, 13th International Child Neurology Congress, Foz do Iguazu, Brazil, May 4-8, 2014.

Obermeier P, Karsch K, Seeber L, Schneider J, Muehlhans S, Chen X, F Tief, Kaindl A, Weschke B, Böttcher S, Diedrich S, Rath B. *Ein gesicherter Fall akuter disseminierter Encephalomyelitis (ADEM) bei einer 5-jährigen Patientin mit humaner Parechovirus-Infektion [A confirmed case of acute disseminated encephalomyelitis (ADEM) in a 5-year-old patient with human parechovirus infection]*. Oral Presentation, 8th Clinical Virology Workshop of the Gesellschaft für Virologie [German Society for Virology], Würzburg, Germany, November 7-8, 2014.

Obermeier P, Karsch K, Chen X, Miera O, Peters B, Francis RC, Amann V, Duwe S, Fraaij P, Heider A, de Zwart M, Berger F, Osterhaus A, Schweiger B, Rath B. *Oseltamivir Pharmakokinetik unter Hämofiltration und Organersatzverfahren [Pharmacokinetics of oral and intravenous oseltamivir treatment of severe influenza B infection requiring organ replacement therapy]*. Oral Presentation, 7th Clinical Virology Workshop of the Gesellschaft für Virologie [German Society for Virology], Würzburg, Germany, November 7-8, 2013.

Seeber L, Conrad T, Klokow M, Raetze A, Hoppe C, **Obermeier P**, Chen X, Karsch K, Muehlhans S, Boettcher S, Diedrich S, Schweiger B, Rath B. *Improving Vaccine Preventable Disease Surveillance with Evidence-based Digital Vaccination Records*. Poster Presentation, 31st Annual Clinical Virology Symposium, Daytona, FL, USA, April 26-29, 2015.

Seeber L, Conrad T, Klokow M, Raetze A, Hoppe C, **Obermeier P**, Chen X, Karsch K, Muehlhans S, Rath B. *Wie gut wissen Eltern über den Impfstatus ihrer Kinder Bescheid? Ein digitaler Lösungsvorschlag [Do parents know the vaccination status in their children? – proposing a digital solution]*. Oral Presentation, 5th German Influenza Conference, Erfurt, Germany, September 17-19, 2015.

Tief F, Hoppe C, Seeber L, **Obermeier P**, Chen X, Karsch K, Muehlhans S, Adamou E, Conrad T, Schweiger B, Adam T, Rath B. *Pneumokokken und Influenza - wie häufig sind Koinfektionen bei Kindern mit grippalen Infekten? [Pneumococcus and Influenza – How Common are Coinfections in Children with ILI?]*. Oral Presentation, 5th German Influenza Conference, Erfurt, Germany, September 17-19, 2015.

Seeber L, Karsch K, Schneider J, **Obermeier P**, Chen X, Tief F, Muehlhans S, Kaindl A, Böttcher S, Diedrich S, Rath B. *Human parechovirus (HPeV) infections: Case report of hPeV-associated acute disseminated encephalomyelitis (ADEM) and syndromic surveillance in 284 children with CNS-infections*. Poster Presentation, 32nd Annual Meeting

of the European Society for Paediatric Infectious Diseases (ESPID), Dublin, Ireland, May 6-10, 2014.

Grover S, Hoppe C, Adamou E, Tief F, Karsch K, Muehlhans S, **Obermeier P**, Chen X, Seeber L, Behrens S, Reiche J, Schweiger B, Rath B. *Wheezing Following Acute Respiratory Infections Versus Immunization in Young Children*. Poster Presentation, ISIRV Antiviral Group Conference 'Influenza and Other Respiratory Virus Infections: Advances in Clinical Management', Tokyo, Japan, June 4-6, 2014.

Grover S, Weick S, **Obermeier P**, Chen X, Seeber L, Tief F, Karsch K, Muehlhans S, Hoppe C, Adamou E, Behrens S, Reiche J, Schweiger B, Rath B. *Seizure Following Respiratory Viral Infection Versus Immunization in Infants and Children – a Syndromic Surveillance Study*. Poster Presentation, The 5th ESWI Influenza Conference, Riga, Latvia, September 14-17, 2014.

Seeber L, Conrad T, Klokow M, Raetze A, Hoppe C, **Obermeier P**, Chen X, Karsch K, Muehlhans S, Rath B. *Wie gut sind Eltern über den Impfstatus ihres Kindes informiert? [Are parents adequately informed about the vaccination status of their children?]*. Oral Presentation, 8th Clinical Virology Workshop of the Gesellschaft für Virologie [German Society for Virology], Würzburg, Germany, November 7-8, 2014.

Rath B, Chen X, Seeber L, **Obermeier P**, Karsch K, Tief F, Tuttle RC, Muehlhans S, Peiser C, Duwe S, Schweiger B. *Evaluation of a Novel Second-Generation Rapid RSV Test at the Point-of-Care*. Poster Presentation, 9th International Respiratory Syncytial Virus Symposium, Stellenbosch, South Africa, 9-13 November, 2014.

Rath B, Chen X, Karsch K, Schwarz W, Seeber L, **Obermeier P**, Muehlhans S, Tief F, Conrad T, Schweiger B. *Unusual Presentations of Infuenza A/A and A/B Dual Infections – The Charité Influenza-Like Disease (=ChILD) Cohort*. Poster Presentation, The XV International Symposium on Respiratory Viral Infections, Rotterdam, The Netherlands, March 14-17, 2013.

Chen X, **Obermeier P**, Tief F, Muehlhans S, Karsch K, Seeber L, Wählisch S, Duwe S, Yousef K, von Kleist M, Schweiger B, Rath B. *Rapid Follow-up testing for the monitoring of influenza infections in infants and children*. Poster Presentation, 29th Clinical Virology Symposium, Daytona, FL, USA, April 27 –May 2, 2013.

Rath B, Muehlhans S, Tief F, Karsch K, **Obermeier P**, Chen X, Seeber L, Adamou E, Peiser C, Schweiger B. *Simultaneous influenza and RSV point-of-care diagnostics using innovative fluorescence-based rapid testing*. Poster Presentation, 29th Clinical Virology Symposium, Daytona, FL, USA, April 27 –May 2, 2013.

Karsch K, **Obermeier P**, Seeber S, Chen X, Tief F, Muehlhans S, Schwarz W, Hoppe C, Conrad T, Böttcher S, Diedrich S, Rath B. *Prevalence and clinical characteristics of pediatric parechovirus infections – the Meningitis Surveillance at Charité (=MenSCh) Cohort*. Poster Presentation, 29th Clinical Virology Symposium, Daytona, FL, USA, April 27 –May 2, 2013.

Chen X, Pouran-Yousef K, Wählisch S, **Obermeier P**, Tief F, Muehlhans S, Seeber L, Karsch K, Duwe S, von Kleist M, Schweiger B, Rath B. *Quantitative influenza diagnostic testing (QIDT) as a novel biomarker for the monitoring of disease activity at the point-of-care*. Oral Presentation, Options for the Control of Influenza VIII Conference, Cape Town, South Africa, September 5-10, 2013.

Tief F, Hoppe C, Seeber L, **Obermeier P**, Chen X, Karsch K, Muehlhans S, Adamou E, Conrad T, Schweiger B, Adam T, Rath B. *Impact of pneumococcal co-infection on disease severity and antibiotic prescriptions in infants and children with influenza: an inception cohort study*. Oral Presentation, Options for the Control of Influenza VIII Conference, Cape Town, South Africa, September 5-10, 2013.

Karsch K, **Obermeier P**, Seeber L, Chen X, Tief F, Muehlhans S, Hoppe C, Conrad T, Böttcher S, Diedrich S, Rath B. *Prospektive Surveillance von humanen Parechoviren bei*

hospitalisierten Kindern mit ZNS-Infektionen. Die Meningitis Surveillance at Charité (MenSCh) Kohorte [Prospective Surveillance of Human Parechovirus in Hospitalized Children with CNS Infections – The Meningitis Surveillance at Charité (MenSCh) Cohort]. Oral Presentation, 7th Clinical Virology Workshop of the Gesellschaft für Virologie [German Society for Virology], Würzburg, Germany, November 7-8, 2013.

Chen X, Seeber L, **Obermeier P**, Tief F, Muehlhans S, Karsch K, Wählisch S, Duwe S, Pouran-Yousef K, von Kleist M, Schweiger B, Rath B. *Verlaufskontrolle von Influenzainfektionen mithilfe von Schnelltests [Longitudinal following-up of influenza infections with rapid diagnostic testing]*. Oral Presentation, 7th Clinical Virology Workshop of the Gesellschaft für Virologie [German Society for Virology], Würzburg, Germany, November 7-8, 2013.

Rath B, **Obermeier P**, Tief F, Karsch K, Tuerk E, Muehlhans S, Schweiger B. *Timely Detection of Influenza A&B Infection in Infants and Children using Conventional and Fluorescence-based Rapid Testing*. Panel presentation, 28th Clinical Virology Symposium, Daytona, FL, USA, April 22-25, 2012.

Tuerk E, Kaufmann S, Goergen, **Obermeier P**, Tief F, Karsch K, Muehlhans S, Duwe S, Schweiger B, Rath B. *Early Diagnosis of Influenza A&B Infection in Infants and Children using Fluorescence-based Rapid Testing*. Poster presentation, 28th Clinical Virology Symposium, Daytona, FL, USA, April 22-25, 2012.

Acknowledgements

In the first instance, I would like to express my sincere gratitude to my supervisor Dr. Barbara Rath who provided me with the opportunity to gain in-depth experience in high-impact clinical research in pediatric infectious diseases and public health surveillance. At all times, Dr. Rath has unswervingly provided our team with valuable advice, always emphasizing the importance of transparency, open communication, accuracy, integrity and endurance as the key prerequisites for sustained success in translational research. Her expertise as well as her dedication and commitment to her patients and their families, are remarkable. Secondly, I want to thank and commemorate Prof. Dr. Gerhard Gaedicke, former head of the Department of General Pediatrics at the Charité University Medical Center and senior member of the Dieter Scheffner Center for promoting and supporting our learning research experience as medical students. Being my very first teacher in medical school, he has left a lasting positive impression on me by imperturbably reinforcing the importance of teamwork. This work was considerably influenced and supported by our long-term collaborators at the Robert-Koch-Institute who provided virologic analyses at the National Reference Center for Poliomyelitis and Enteroviruses in kind to our team throughout several years. In this context I want to thank Dr. Schweiger, as well as Dr. Sabine Diedrich and Dr. Sindy Boettcher in particular for providing me insight into the world of laboratory science in addition to the clinical research experience. To the bioinformatical end of our work, I am very grateful to our collaborative partner at the Freie University Berlin, Prof. Dr. Tim Conrad, who was always ready to support me when I had data analysis questions and who provided us with sophisticated bioinformatics analyses. I would like to extend my thanks to all my team members, most of all to Susann Muehlhans, Franziska Tief, Xi Chen, Lea Seeber, Katharina Karsch, Maren Alchikh, and Christian Hoppe. With your advice and encouraging words and your dedication to a trustful relationship and a great work environment, the true meaning of team spirit became evident to me at all times. To my family, I owe a lot for their understanding, patience, and support in every aspect of my studies. For me, it is beyond words how much I have appreciated the loving care of my parents, Anna-Maria and Johannes. Moreover, I am so thankful for the support that I have received from so many thoughtful people – especially from Christina, Dieter, Andreas, and Jeffrey.