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

DISSERTATION

Enhancing Vaccine Safety Monitoring and the Accurate Reporting and Differential Diagnosis of Adverse Events in Clinical Research and the Pediatric Acute Care Setting

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

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Susann Mühlhans

aus Radebeul

Datum der Promotion: 09.09.2016

Table of Content

Abbreviations

AE	Adverse Event
AEFI	Adverse Event Following Immunization
BC	Brighton Collaboration
CDC	Center for Diseases Control
CIOMS	Council for International Organizations of Medical Sciences
DLR	Diagnostic Likelihood Ratio
FDA	Food and Drug Administration
HCP	Health Care Professional
NPV	Negative Predictive Value
PCR	Polymerase Chain Reaction
PEI	Paul Ehrlich Institute
POC	Point Of Care
PPV	Positive Predictive Value
QM	Quality Management
RCT	Randomized Clinical Trial
RKI	Robert Koch Institute
RSV	Respiratory Syncytial Virus
WHO	World Health Organization

Abstract

Einleitung Präzise und zeitgerechte Meldungen von unerwarteten Ereignissen nach Impfung (UENI) sind entscheidend für die Auswertung von Impfsicherheitssignalen. Bevor ein kausaler Zusammenhang zwischen der verabreichten Impfung und dem Ereignis untersucht werden kann, muss dieses durch z.B. definierte Falldefinitionen erhoben werden. Typische pädiatrische Symptome, wie Fieber und Influenza-ähnliche Erkrankungen werden in der Pädiatrie oft als UENI fehlinterpretiert. *Methodik* Wir erstellten eine systematische Übersicht (Medline, Embase, 1989-2011) welche die Verwendung von Falldefinitionen zur Erhebung von Impfsicherheitssignalen in randomisierten, klinischen Studien in Entwicklungsländern analysiert. Eine Onlineumfrage unter Mitgliedern der Deutschen und Russischen pädiatrischen Berufsverbänden, untersuchte die Integrierung einer formalen Impfausbildung in der pädiatrischen Weiterbildung, die Kenntnis von Meldewegen sowie die Nutzung von Falldefinitionen zur Erhebung von UENI. An der Charité wurde der Nutzen von Influenza- und RSV-Schnelltests zur Differenzierung eines UENI von einer natürlichen Infektion untersucht. *Ergebnisse* In 70% der 50 Impfsicherheitsstudien wurde mindestens eine Falldefinition genutzt. Fieber wurde am häufigsten definiert; 16 verschiedene Fieberdefinitionen wurden verzeichnet. Die logistische Regressionsanalyse zeigte eine positive Korrelation zwischen der Verwendung einer beliebigen Fieberdefinition und der Wahrscheinlichkeit Fieber als ein UENI zu detektieren ($p = 0.027$). Unter 1.632 analysierten Onlinefragebögen zeigte sich, dass Pädiater mehr als eine Stunde pro Arbeitstag für die Impfberatung aufwenden, obwohl die Mehrheit (57%) keine Impfausbildung erhielt. Korrekte Meldewege für UENI kannten 35%, Falldefinitionen nur ein Drittel der Befragten. Impfsicherheitsgeschulte Pädiater wendeten signifikant häufiger Falldefinitionen und korrekte Meldewege an ($p < 0.05$). Fluoreszenz-basierte Influenza- und RSV-Schnelltests (SOFIA™) wurden mit Immunoassay-basierten Schnelltests (QuickVue™) verglichen; als Goldstandard diente die am Robert Koch Institut durchgeführte quantitative Echtzeit-PCR. Fluoreszenz-basierte Schnelltests zeigten höhere Sensitivitäten/Spezifitäten für RSV (78.6/93.9%), Influenza A (80.6/99.3%) und Influenza B (71.9/99.0%). *Schlussfolgerung* Die Analyse von Impfsicherheitssignalen ist stark von der exakten Erhebung von UENI abhängig. Durch die Optimierung vorhandener, internationaler Impfsicherheitsstandards können Metaanalysen zahlreicher Impfsicherheitsdaten vereinfacht und somit seltene UENI besser detektiert werden. Zuverlässige fluoreszenz-basierte Influenza- und RSV-Schnelltests stellen eine sinnvolle Ergänzung zur Impfsicherheitskommunikation in der pädiatrischen Grundversorgung dar. Eine pädiatrische Impfausbildung ist unbedingt erforderlich, um das Wissen um die Meldung von UENI, in Zulassungsstudien und auch Anwendungsbeobachtungen von Impfstoffen, zu stärken.

Abstract

Introduction Accurate and timely reporting of adverse events following immunization (AEFI) is key to vaccine safety surveillance. Before the causality of a presumed AEFI can be investigated, the AEFI need to be 'ascertained', i.e. mapped to pre-defined case definitions. Common symptoms in pediatrics, such as fever and influenza-like-illness are often mistaken for AEFI. *Methods* We conducted a systematic review (Medline, Embase, 1989–2011) of developing country randomized clinical vaccine trials (RCT) studying utilization of case definitions for the reporting of safety outcomes. We also conducted a 31-item online questionnaire among members of the German and Russian Professional Pediatric Associations, assessing exposure to vaccine safety training, awareness of reporting pathways and utilization of case definitions. At Charité, we tested the value of point-of-care diagnostics for influenza and RSV as a means of differentiating "natural infection" from AEFI. *Results* In 50 vaccine safety clinical trials, 70% used at least one case definition. The most commonly defined AEFI was fever, but 16 different fever case definitions were used. Logistic regression showed a positive correlation between implementation of *any* fever case definition with the likelihood of detecting fever as an AEFI ($p = 0.027$). Analysis of 1.632 online questionnaires from German and Russian pediatricians revealed that at least one hour per workday was spent on vaccine consultations, even though the majority (57%) had never received any vaccine safety training. Accurate AEFI reporting pathways were known to 35%, case definitions to only one-third. Pediatricians who had been trained in vaccine safety, were significantly more likely to apply case definitions and to report AEFI accurately ($p < 0.05$). Novel fluorescence-labeled point-of-care tests for influenza and RSV (SOFIA™) were compared to "traditional" rapid tests, (QuickVue^{TM}) using real-time PCR at the Robert Koch Institute as gold standard. Novel, fluorescence-based SOFIA^{TM} tests showed increased sensitivities/specificities of RSV (78.6/93.9%), Influenza A (80.6/99.3%) and Influenza B (71.9/99.0%) compared to real-time PCR. *Conclusion* Vaccine safety reporting relies on accurate AEFI ascertainment. International standards are available and should be streamlined to facilitate the pooled analysis of large numbers of vaccine safety data across sites, ensuring 'meta-analyzability' and the detection of rare AEFI. Second-generation point-of-care tests for influenza and RSV provide highly accurate results assisting in the timely vaccine safety communication in the acute care setting. Formal vaccine safety training is urgently needed to strengthen pediatric core competencies for AEFI reporting and the accurate conduct of vaccine clinical trials.

1. Introduction

Trust in Vaccines and Vaccine Safety Monitoring

Vaccines are among the most effective public health measures helping to maintain health and to prevent morbidity and mortality (1). Routine immunizations are mainly administered during childhood to prevent infections and the transmission of infectious diseases (2). The fear of adverse events (AE) is usually greater with regards to immunization than to drugs, as vaccines are typically administered to healthy individuals. The occurrence of real or perceived adverse events following immunization (AEFI) may diminish levels of trust in vaccines. The mass media may further amplify fears, rumors and uncertainties (3), (4).

Physicians' Reporting of Adverse Events Following Immunization

O'Leary et al. concluded from a survey they conducted, that more and more physicians are themselves losing confidence in the safety of vaccines, especially during pre-licensure vaccine clinical trials (5). The adequate conduct of pre- and post-marketing studies is equally essential, combined with transparent and accurate but understandable communication of the outcomes of such studies (6).

Parents tend to rely on pediatricians with questions and concerns about vaccine safety (7), (8). It has been shown that parental trust in vaccines is highly dependent on a healthy doctor-patient relationship (9). Pediatricians working in the frontlines in primary health care settings, are usually the ones administering vaccines and, may be the first to encounter AEFI (10), (11). This is the reason why pediatricians play an important role in the timely assessment and reporting of AEFI to the respective vaccine-pharmacovigilance agency such as the Food and Drug Administration (FDA) in the United States and the Paul-Ehrlich Institute (PEI) in Germany (12).

Causality Assessment for Adverse Events Following Immunization

The global monitoring of AEFI, however, is in the hands of the World Health Organization (WHO). In March 2013, WHO published a revised user manual and *aide-mémoire* providing an algorithm to assist with systematic, standardized AEFI *causality* assessment to be used by regulatory authorities, pharmacovigilance or surveillance departments in national immunization programs (13). A recently published editorial highlighted that despite these global coordination efforts, uniform AEFI causality assessment methodologies were practically nonexistent in the biomedical literature (PubMed) published between 1989 and 2014 (14). The purpose of the WHO algorithm is to assist the assessor in the rapid evaluation of the likelihood of a causal association between a particular AE and the vaccine administered to the respective patient. Depending on the quality of the information available regarding the AE in question, three levels of association are defined as follows: A) Consistent causal association, B) Intermediate causal association, and C)

Inconsistent causal association (coincident event); if adequate data are missing, the event has to be considered as "unclassifiable" (13).

Ascertainment of Adverse Events Following Immunization

Before causality can be assessed however, it must be ascertained whether or not an AE has occurred in the first place (AEFI ascertainment). The AEFI causality assessment is usually based on individual patient data and is highly dependent on the quality of the respective AEFI report. This implies that the physicians who may encounter AEFI must be trained in AEFI ascertainment and reporting, including the compliance with international case definitions and reporting guidelines. Studies have shown that the quality of AEFI reports originating from health care professionals (HCP) is in fact unsatisfactory (15). Adherence to published vaccine pharmacovigilance terminologies issued by the Council for International Organizations of Medical Sciences (CIOMS), the WHO, the Brighton Collaboration (BC) and others will ensure a common language in AEFI reporting and ascertainment (16).

Adapting Vaccine Safety Monitoring Systems for Developing Countries

The rapid development of new vaccines in developing countries against common childhood diseases, and the gradual emergence of clinical trial infrastructure in developing countries provide new opportunities. With this clinical trial infrastructure in place, there is increased demand for standardization and alignment with terminologies and algorithms used in different parts of the world (17), (18). This work provides a first insight focused on vaccine safety clinical research in low-resource settings, to identify gaps and progress made with regard to an expanding international vaccine safety infrastructure.

Vaccine Safety Training among Health Care Professionals

Pediatricians should use existing guidelines as a desk reference to improve the quality of AEFI reports and hereby, the quality of post-marketing surveillances. A survey conducted by Zanoni et al. in 2009 investigated vaccine safety monitoring programs across 26 European countries and stated that only 35% of participating countries had developed training programs providing guidance to HCP (19). The authors concluded an urgent need to improve vaccine safety training, teaching HCP to ascertain and report AEFI accurately.

To obtain detailed data on the current situation in Germany and Russia as a comparator, this work investigated whether pediatricians had ever received any vaccine safety training during their medical education and specialization. The goal was to identify knowledge gaps in vaccine safety reporting practices in pediatric health care settings directing the development of new training programs in teaching vaccine safety standards and communication skills among HCP.

Differential Diagnosis of Adverse Events Following Immunization

Any physician taking a comprehensive medical history should inquire about any previous AEFI (if applicable) and any underlying conditions (i.e. allergies, genetic disorders, drug habits, preceding surgical procedures or traumata). A comprehensive vaccination and exposure history should be followed by a complete physical examination to rule out any concomitant AE or illness. During early childhood, when the majority of routine immunizations are administered, the most common concurrent illness may be an acute infectious disease, mostly viral in origin, and typically occurring 4-8 times per year in infants and toddlers (20). These infections are usually coincidental and may be unapparent before or at the time of immunization and thus create considerable confusion when assessing the tolerability of routine childhood vaccines (21).

The Role of Rapid Diagnostics in Vaccine Safety Monitoring

Influenza viruses and respiratory syncytial viruses (RSV) are among the most common causes of respiratory viral illness leading to hospitalization in this age group (22), (23). In early childhood, acute respiratory infections and influenza-like illness are common and may be accompanied by nonspecific symptoms such as fever, headache, cough, and fatigue, rash, malaise, vomiting, and others. Any of these signs, when occurring within the first days after immunization, may be mistaken for AEFI (24)-(26). The timely confirmation of ongoing infections with influenza or RSV has now become possible with the development of highly sensitive and specific rapid diagnostic methods. Ruling-out infectious triggers of AE constitutes an important step in AEFI causality assessments. In the acute care setting, rapid diagnostics open the opportunity for improved communication with concerned parents. In the past, the utility of influenza and RSV point of care (POC) testing in clinical practice has been debated, as reported sensitivities varied widely (27)-(32).

Objectives

This work addresses three key aspects of the complex issue of international vaccine safety monitoring and reporting: the implementation of AEFI definitions in randomized clinical trials (RCT), the AEFI reporting in everyday clinical practice and the usefulness of POC diagnostics as a concrete measure to improve the monitoring of vaccine preventable diseases and vaccine safety and to achieve greater accuracy in vaccine communication in pediatric acute care settings.

1) We conducted a systematic literature review analyzing the utilization of standardized definitions in vaccine safety RCT in low- and middle-income countries.
2) In collaboration with Pediatric Professional Associations in Germany and Russia, we conducted an online survey assessing AEFI ascertainment and reporting practices in different health care settings and the role of vaccine safety training during medical school or

postgraduate training. The German and Russian pediatric societies were chosen because of the differences in the educational system in both countries. The Russian "academy system" allows students to focus on pediatrics from the beginning of their medical studies, whereas German students complete six years of general medical school before specializing in pediatrics during residency training.

3) For the timely differential diagnosis of common infectious diseases of childhood versus AEFI at the patients' individual level, we evaluated a conventional laminar flow test for the detection of influenza and RSV (QuickVue™) compared to an second generation fluorescence-based rapid antigen detection assay (SOFIA™) at the pediatric POC at Charité, compared to standardized real-time PCR assays.
4) To provide additional opportunities for vaccinology training during medical school electives, an innovative teaching program was implemented for interested students at Charité, which allows them to receive formal training in vaccinology.

2. Methods

2.1. Systematic Review

To assess the situation in RCT in low- and middle-income countries, a systematic literature review was conducted. Medline and Embase (1989–2011) were screened on 31 October 2011 for developing country RCT, reporting safety outcomes with ≥ 50% developing country participation. Developing country vaccine RCT were analyzed with respect to the number of participants, age groups studied, inclusion of safety information, number of reported AEFI, type and duration of safety follow-up, and the use of standardized AEFI case definitions.

2.2. Online Survey among Pediatricians in Germany and Russia

An online survey among members of the German and Russian Professional Pediatric Associations was conducted, analyzing AEFI ascertainment and reporting practices in different health care settings. In May 2011, a 31-item online vaccine safety questionnaire was sent to members of the German Professional Association for Pediatricians (Berufsverband der Kinder- und Jugendärzte, BVKJ) and the Union of Pediatricians of Russia (UPR), via membership mailing list servers in German and Russian. The survey instrument captured information on vaccine safety training, the amount of time spent on vaccine safety consultations, awareness of AEFI reporting pathways, and use of standardized definitions for the ascertainment of AEFI. Participants were also provided with a checklist of potential sources of information on vaccine safety and reporting pathways.

2.3.Influenza and RSV Rapid Testing at the Point of Care

The evaluation of both rapid testing methods was carried out in the context of the IRB approved influenza quality management (QM) program at the Charité Department of Pediatrics, Berlin, Germany in collaboration with the National Reference Center for Influenza at the Robert Koch Institute (RKI) (33). Pediatric inpatients at Charité and children (aged 0–18 years) presenting to the pediatric emergency rooms were screened once a week based on predefined criteria, defined as fever ≥ 38°C and one or more signs/symptoms of respiratory tract infection. Screening and rapid testing of nasal and nasopharyngeal samples were performed in real-time by a specifically trained independent QM team. For validation of rapid test results, real-time PCR was performed at the National Reference Centre for Influenza at the RKI (34).

2.3.1. First Generation Rapid Testing - QuickVue™ Influenza A+B and RSV10

Between January 2010 and April 2011 nasopharyngeal swabs/aspirates underwent immediate and simultaneous rapid testing using the QuickVue™ Influenza A+B and RSV10 (Quidel) dipstick immunoassays according to the manufacturer's protocol.

2.3.2. Second Generation Rapid Testing - SOFIA™ Influenza A+B and RSV

Between November 2011 and March 2012 and from December 2012 to April 2013 rapid testing via SOFIA™ Influenza A+B and RSV test kits (Quidel) was performed, which as well employed a lateral-flow immunofluorescence technique interpreted with the SOFIA™ analyzer. Testing was performed according to the manufacturer's protocol.

2.4.Vaccine Safety Communication Training at Charité University

During the winter semester 2010/11 a specific 3-week *Modular Training Program in Vaccine Safety & Communication* was implemented, including intense training with a mixture of teaching sessions associated with practical applications in small group settings and combined with e-learning features, interviews and consultations with parents and children on the topic of vaccine safety as well as evidence-based literature training and regular evaluations.

3. Results

3.1.Safety Reporting in Developing Country Vaccine Clinical Trials

The systematic search yielded a total number of 50 RCT reporting safety outcomes. A total number of 446,908 participants were enrolled. Overall 735,920 vaccine doses were administered, with an average of 1.64 vaccine doses administered/participant. Only 12/50 trials enrolled more than 3,000 subjects, 11 trials had more than 10,000 participants. Nearly two-thirds (64%) of the developing country vaccine RCT were conducted in children (0–18 years) with three out of four pediatric

vaccine trial restricted to infants (0–1 year). Of note, 66% of these infant vaccine trials did not report any AEFI during the follow-up period. In 56% of all RCT publications, AEFI assessments and AEFI reporting were conducted by HCP, the remaining 44% did not name the profession of the individual responsible for safety surveillance and reporting. The duration of follow-up was specified in 49/50 vaccine RCT publications and ranged from 3 days to 2 years (mean 73 days, median 56 days). Safety follow-up however, was not always differentiated from follow-up for efficacy endpoints. The majority (62%) of the long-term follow-up visits were conducted in person. In 23/50 developing country vaccine RCT publications, an additional immediate safety observation was performed after immunization ranging from 15 to 60 min (mean 16.9 min, median 30 min). In 70% (35/50) of all RCT listed in our review, at least one AEFI definition was used. The most commonly defined AEFI was fever, followed by local and systemic reactions. Logistic regression analysis revealed a positive correlation between the implementation of any fever case definition and the reporting rate for fever as an AEFI (p = 0.027).

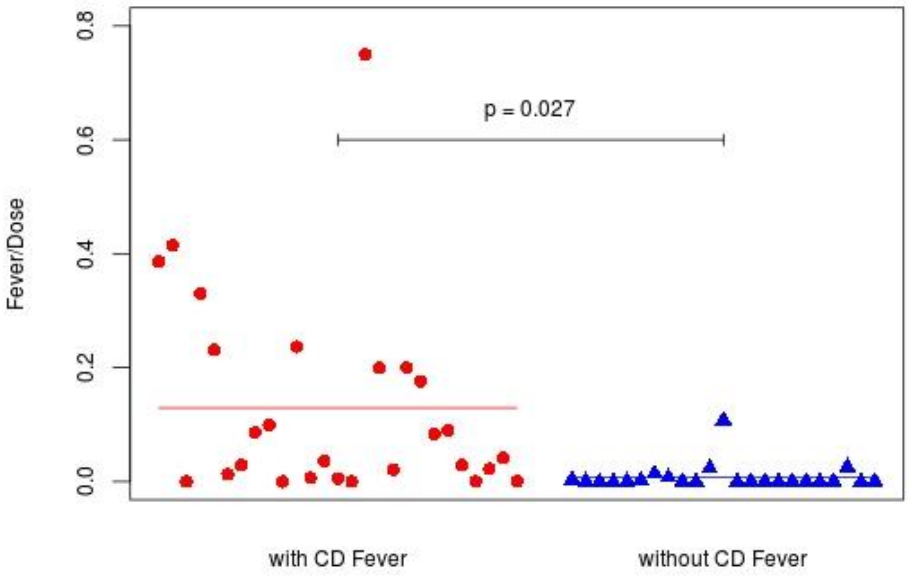

Figure 1 - Reporting rates for fever as an AEFI (per vaccine dose administered) in RCT with and without the use of fever case definition (CD)

Overall, 16 different definitions for fever were applied, indicating a significant lack of standardization. Predefined AEFI definitions as issued by the BC and endorsed by WHO and other regulatory authorities, were used in only 2/50 RCT.

3.2.Awareness and Utilization of Reporting Standards for AEFI

A total of 1,632 pediatricians in Germany and Russia completed the online questionnaire with 808 German and 824 Russian completed surveys. Among surveyed pediatricians, 98.9% are spending

nearly one hour per workday on vaccine safety consultations. Nevertheless, the majority of surveyed pediatricians (56.7%) had never received any formal vaccine safety training during medical or postgraduate training. About half of the Russian participants (55.3%, $p < 0.01$) had been exposed to formal vaccine safety training, compared with only one-quarter of German participants (26%, $p < 0.01$). This comparison was of interest as the Russian Academy System allows students to specialize in pediatrics from the first year of medical studies onwards, rather than *after* graduation from medical school, as is the case in Germany. Russian and German pediatricians uniformly named their pediatric association as the preferred source of vaccine safety information, followed by the Ministry of Health (both at the $p < 0.05$ level). When asked which would be the accurate AEFI reporting pathway in their country, only 35% of participating pediatricians (29/39% in Germany/Russia) were able to name the national regulatory agency in charge of vaccine-pharmacovigilance. The majority (65%) would report to other institutions, resulting either in significant delay of safety reports (20/21% in Germany/Russia) or complete loss (51/40% in Germany/Russia). AEFI (real or perceived) had been observed by 68% of all survey participants. Two-thirds were either unaware of, or unwilling to use, AEFI ascertainment criteria (Figure 2).

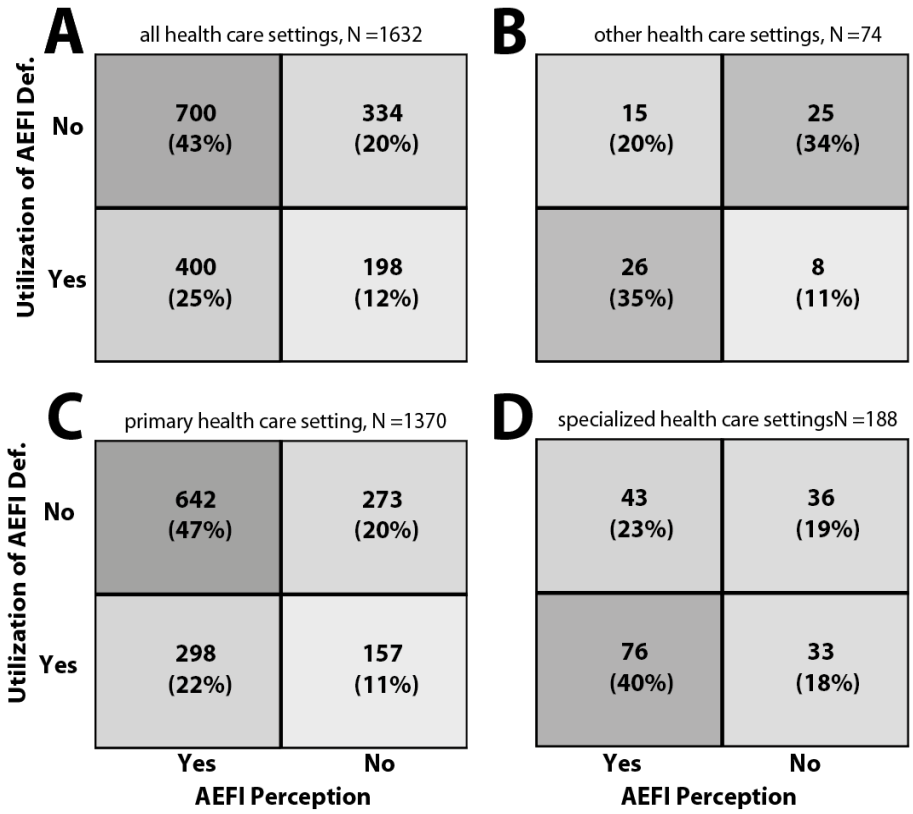

Figure 2 – AEFI ascertainment using case definitions [utilization of AEFI definitions (Def.)] in relation to AEFI perception. A) All health care settings B) Other health care settings C) Primary health care settings D) Specialized health care settings. Each field in the two-by-two table illustrates the total number and percentage of pediatricians working in different health care settings in relation to utilization of AEFI definitions (y-axis) and AEFI perception (x-axis)

Among pediatricians unwilling to use standardized criteria for case ascertainment, 70% reported having previously encountered AEFI in clinical practice. Again, primary care pediatricians were most likely to have encountered AEFI, but were the least likely group to utilize AEFI case definitions ($p < 0.01$). There was a significant association between formal vaccine safety training and knowledge of accurate AEFI reporting pathways ($p < 0.05$). Training had a significant impact on the utilization of standardized AEFI definitions in pediatric primary care ($p < 0.001$). Most pediatricians utilizing AEFI definitions had received vaccine safety training during pediatric specialization (26.3%) and medical studies (23.1%).

3.3.Influenza and RSV Rapid Testing at the Point of Care

3.3.1. QuickVue™ Influenza A + B and RSV10

A total number of 395 consecutive QM cohort subjects were tested at the POC during the 2010/2011 flu season. The sensitivities, specificities, positive predictive value (PPV), negative predictive value (NPV), as well as positive and negative diagnostic likelihood ratios (DLR) are displayed in Table 1.

Table 1 – Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative diagnostic likelihood ratios (DLR) for influenza and RSV in patients <1 year and >1 year of age using QuickVue™ rapid tests at point of care

	All		**<1 year**		**>1 year**	
	Influenza	RSV	Influenza	RSV	Influenza	RSV
Sensitivity (%)	62.7	67.8	76.0	76.2	58.4	47.1
Specificity (%)	98.0	98.5	97.8	97.5	98.1	99.1
PPV (%)	91.4	88.9	86.4	91.4	93.1	80.0
NPV (%)	88.3	94.6	95.8	92.2	82.5	95.9
Positive DLR	30.6	35.2	30.0	45.6	31.0	50.4
Negative DLR	00.4	00.2	00.4	00.3	00.2	00.5

3.3.2. SOFIA™ Influenza A + B and SOFIA™ RSV

During the 2011/2012 flu season 649 nasopharyngeal samples were analyzed using the SOFIA™ Influenza A + B test kit. Key results are depicted in Table 2.

Table 2 – Sensitivity, Specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative diagnostic likelihood ratios (DLR) of the Sofia™ Influenza A+B rapid test in patients <1 and >1 year of age at point of care.

	All	**<1 year**	**>1 year**
Sensitivity (%)	78.1	85.7	76.3
Specificity (%)	99.7	100	99.4
PPV (%)	96.6	100	95.7
NPV (%)	97.3	99.1	96.2
Positive DLR	225	∞	137
Negative DLR	0.220	0.143	0.239

During the 2012/2013 flu season 686 nasopharyngeal samples were analyzed using the SOFIA™ RSV test kit. Key results are depicted in Table 3.

Table 3 - Sensitivity, Specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative diagnostic likelihood ratios (DLR) of the Sofia™ RSV rapid test in patients <2 years and ≥2 years of age at point of care.

	All	**<2 years**	**≥2 years**
Sensitivity (%)	78.6	81.8	68.6
Specificity (%)	93.9	92.4	95.2
PPV (%)	77.6	82.6	63.2
NPV (%)	94.2	92.0	96.2
Positive DLR	12.9	10.8	14.3
Negative DLR	0.23	0.20	0.33

3.4.Vaccine Safety Communication Training at Charité University

During the establishment of a vaccine safety elective at Charité, the following key elements have been identified as basic skills that need to be taught to medical students:

- Building and strengthening factual knowledge about different types of vaccines, adjuvants and vaccine delivery methods; accurate vaccination techniques and correct documentation according to WHO standards (35).
- Evaluation of AEFI standardized case definitions and internationally approved reporting pathways; generating awareness of vaccine safety organizations and key stakeholders.
- Knowledge of the aims of different immunization programs; generating an interest in global and public health impacts of vaccines; awareness of national and international guidelines with respect to vaccines and vaccine safety.
- Making immunization status checks an integral part of routine medical practice.
- Learning historical aspects of vaccine development including the implementation and advancement of different vaccination schedules; discussing the path from licensure of new vaccines to official recommendations by regulatory authorities.
- Discussing pros and cons of vaccines to argue about anti-vaccine movements; learning to conduct an open dialogue with parents expressing vaccine hesitancy.

4. Discussion

Lessons to be learned from Developing Country Vaccine Clinical Trials

With the conducted systematic review, several key areas were identified for developing country vaccine RCT that would benefit from capacity building with regards to knowledge transfer and standardization. These include the need for international consensus on the duration of follow-up periods and safety surveillance methodologies, in alignment with the Consolidated Standards of Reporting Trials (CONSORT) Statement for drug trials, as well as initiatives to optimize sample size in safety trials, such that rare AEFI can be detected with sufficient certainty (36). Teaching clinical investigators the consistent utilization of AEFI case definitions will be a key component.

Adjusting Vaccine Safety Follow-Up Periods and Patient Sample Sizes

It is surprising that all 50 reviewed vaccine RCT assessed the respective vaccine to be "safe" even though 82% reported at least one AEFI. Although guidance exists on the optimum sample size in clinical trials testing, not all of the reviewed RCT had a sufficient sample size to detect "rare AEFI" (defined according to CIOMS/WHO) (16). During post-marketing surveillance, even higher sample sizes can be achieved and thus rare AEFI would be more likely to be detected. To increase the sensitivity of post-marketing surveillance, further methodologies should be harmonized with pre-licensure clinical trials. Safety follow-up periods in vaccine RCT were highly inconsistent, ranging from 3 days to 2 years. Because different AEFI may be expected to appear relatively soon after immunization whereas others will occur with some delay, immediate and mid/long-term safety follow-up are equally important. Furthermore, vaccine safety surveillance strategies should be complemented by active screening methodologies such as home/hospital visits or structured remote follow-up via internet or telephone, both conducted by trained HCP, as requested also by Crawford et al. and others (37), (38). Subsequent to publication of our systematic review three additional publications focused on the need to improve standardization and reporting methodologies in developing countries (17), (39), (40). User-friendly technical aids, assisting the HCP with mobile phone or tablet applications, may further facilitate the monitoring process of vaccine safety, especially in low-resource settings (41)-(44).

Consistent Use of AEFI Case Definitions

Vaccine safety surveillance is challenging: large amounts of individual patient data need to be pooled to detect rare, but serious AEFI. AEFI definitions should be standardized; to be helpful at all they have to be applied very consistently over time, allowing comparability of vaccine safety data across different sites and meta-analysis of RCT. Case definitions for fever showed the highest degree of variability with 16 different definitions used. Logistic regression analysis revealed a positive correlation between the implementation of a fever case definition and the reporting rates

for fever as an AEFI ($p = 0.027$). This means that in the absence of AEFI case criteria, important AEFI may go unnoticed. The findings that only one-third of pediatricians in Germany and Russia had ever ascertained AEFI according to international standards, but that trained physicians were more likely to know how and where to report AEFI accurately, demonstrate significant room for improvement through focused vaccine safety training. These results are in line with a recent qualitative study among HCP in Australia (45). The Patient-Reported Outcomes Safety Event Reporting (PROSPER) Consortium has taken the initiative to crosslink industry, regulatory authorities, academics, private sector and patient representatives to implement guidelines for the monitoring of AE (46). Simplification of safety standards as proposed by WHO, FDA, European Medicines Agency, the Centers for Disease Control (CDC), the BC and others, as well as interdisciplinary collaboration are urgently needed to ensure the timely detection, ascertainment, and reporting of AEFI in different parts of the world and during different phases of clinical research and post-licensure surveillance.

WHO Causality Assessment Mechanisms for Adverse Events Following Immunization

Between 2004 and 2009, the CDC-funded Clinical Immunization Safety Assessment (CISA) Network reviewed 76 individual cases of AEFI. Causality assessments were performed using WHO criteria; in nearly one out of four cases, insufficient data made it impossible to perform causality assessments (47). Vaccine-pharmacovigilance data, published by the PEI in Germany in 2013, revealed missing data in 29.2% of 1,778 reported AEFI (48). Incomplete safety data represent a missed opportunity for accurate AEFI causality assessment. The above-mentioned findings are in line with results presented by an Italian inter-regional project of post-marketing surveillance of AEFI, coordinated by the Italian Medicines Agency since 2011. With the introduction of medical training courses for HCP, the number of reported AEFI and the reporting rate per 100,000 administered doses of vaccine increased during two years duration of the Italian project (49). Other vaccine safety monitoring projects in collaboration with national health authorities were established in different parts of the world, providing consultation services, performed by vaccine experts via telephone, fax or e-mail, to improve vaccine risk-benefit communication (50)-(52).

Addressing the Lack of Vaccine Safety Training Programs

The reported survey in Germany and Russia was specifically designed to focus on primary care pediatricians due to their important role in the frontlines of vaccine safety signal detection and reporting to regulatory authorities (53), (54). A recent survey in Australia among parents confirmed that pediatricians are the prime focus point for AEFI reports (55).

The discrepancy between the amount of time spent in daily vaccine safety consultations and the lack of formal vaccine safety training was striking in the survey. The consequences of this lack of training are severe, as this may result in delays or loss of crucial safety reports, as well as failures in standardization and ascertainment of AEFI. The positive news is that exposure to vaccine safety training was significantly linked to accurate AEFI reporting. It can be assumed that the majority of participants volunteering their time to complete a full-length questionnaire belong to a highly motivated group with an active interest in the topic of vaccine safety. Hence, awareness of standards may have been over-reported. Our findings on poor formal vaccine safety training among participating pediatricians are in line with a recent qualitative study conducted by Parella et al. in 2013 that reveals inadequate training among general practitioners and emergency department consultants pre- and post-graduation; all study participants argued in support of improving structured training programs (45). To improve the situation among pediatricians and other HCP, regular vaccine safety training should be obligational, during medical school and beyond, and lifelong learning should be obligational for every physician worldwide. Theoretical principles, including vaccine safety assessment tools and reporting pathways are as important as the acquisition of communication skills. Students should be educated to discuss their questions and concerns openly among peers, including via modern e-learning methodologies and OSCE training in small groups; actual patient/parent encounters may provide participants with the opportunity to practice listening skills and the communication of health messages in real-world situations (56)-(58). The acquisition of knowledge and skills should be verified through pre- and post-course assessments. Trained pediatricians and physicians are in a better position to confidently address questions and concerns voiced by parents and patients. Pediatric professional societies should take a lead in promoting the certification and evaluation of formal vaccine safety training programs. It needs to be emphasized that in many countries, nurses or physician assistants may also administer vaccines and thus should remain actively involved in vaccine safety training initiatives, too (45), (59). Modern e-learning technologies by regulatory agencies, WHO, the CDC, the European Centers of Disease Prevention and Control (ECDC) and others may help to effectively disseminate information on safety standards and communication (60).

Utilization of Sensitive Rapid Diagnostics to Improve Vaccine Safety Communication

Highly sensitive POC tests will help the HCP to provide important health information to parents directly at the time of presentation in the acute care setting. This may help to reassure parents that the patients fever was due to virus, not a vaccine or that the acute respiratory infection within weeks after influenza vaccine administration is in fact, influenza (i.e. vaccination failure) or another virus. For public health authorities, the differential diagnosis will provide critical

information helping to avoid errors such as “inconsistent causal association” of potential AEFI with the administered vaccines, while providing early information if vaccines indeed fail to provide the desired safety or efficacy. Rapid diagnostic testing will be of great advantage at the pediatric POC, but it has to be emphasized that appropriate sample handling and processing will be crucial for the sensitivity and specificity of POC tests (61).

Influenza and RSV Rapid Testing using QuickVue™ and SOFIA™ Systems

For manual reading of tests, the staff should be trained to check for faint signals and control tines and to read the test at the exact time point. Global Solutions of Infectious Diseases (GIS) and others have developed smart phone technologies to help with the validation and digital documentation of classical “strip test results” as they are generated by manually read laminar flow tests such as QuickVue™ and many other tests (62). With the accurate technique, the detection limit can be pushed to its limit. Second-generation tests such as the licensed SOFIA™ test, use fluorescent-tagged antigen signals showing significant improvement over manually read tests. The fluorescent signals show enhanced intensity and are read automatically and punctually, by a fluorescent reader. The sensitivity of influenza and RSV SOFIA™ rapid tests was comparable to studies by other groups (63)-(67). This also represents a significant improvement over previous evaluation of a first-generation test (QuickVue™) in the same QM cohort setting. The sensitivity and the high DLR for RSV and influenza SOFIA™ tests, are in line with the recently issued FDA requirements (80% when using a molecular comparator method) (68). Subsequent to our findings several additional publications stated the importance of improving and implementing POC tests at the forefront of infectious disease control measurements (66), (69). Simultaneous sampling for parallel rapid testing for influenza and RSV under “real-life” conditions at the POC therefore provides timely information for parent consultation and infection control measures in the busy acute care setting.

Summary

We conclude that enhanced vaccine safety monitoring and communication, including accurate reporting and ascertainment of AEFI could therefore be achieved by implementing the following measures:

- Consistent implementation of vaccine safety standards and terminologies and coherent follow-up periods during pre- and post-marketing surveillance.
- Accurate and timely reporting of potential AEFI to vaccine pharmacovigilance authorities.
- Precise causality assessments using the WHO algorithms.
- POC diagnostics of important infectious causes to help distinguish AEFI from vaccination failure and AE due to "natural" causes.
- Intensive vaccine safety training of HCP, including risk communication and evidence-based principles of vaccine safety surveillance and research to improve core competencies early on during medical training and education.

References

1. WHO/UNICEF. Immunization Summary for 2013 Data. 2014. (Accessed June 29, 2015, at http://www.who.int/immunization/monitoring_surveillance/Immunization_Summary_2013.pdf?ua=1).
2. WHO/UNICEF. Global Immunization Data 2013. 2014. (Accessed June 29, 2015, at http://www.who.int/immunization/monitoring_surveillance/global_immunization_data.pdf?ua=1).
3. Tafuri S, Gallone MS, Cappelli MG, Martinelli D, Prato R, Germinario C. Addressing the anti-vaccination movement and the role of HCWs. Vaccine. 2014;32(38):4860-5.
4. Dube E, Vivion M, MacDonald NE. Vaccine hesitancy, vaccine refusal and the anti-vaccine movement: influence, impact and implications. Expert Rev Vaccines. 2015;14(1):99-117.
5. O'Leary ST, Allison MA, Stokley S, Crane LA, Hurley LP, Beaty B, et al. Physicians' confidence in vaccine safety studies. Prev Med. 2013;56(3-4):231-3.
6. Kochhar S. Communicating vaccine safety during the development and introduction of vaccines. Curr Drug Saf. 2015;10(1):55-9.
7. Vannice KS, Salmon DA, Shui I, Omer SB, Kissner J, Edwards KM, et al. Attitudes and beliefs of parents concerned about vaccines: impact of timing of immunization information. Pediatrics. 2011;127 Suppl 1:S120-6.
8. Leask J, Kinnersley P, Jackson C, Cheater F, Bedford H, Rowles G. Communicating with parents about vaccination: a framework for health professionals. BMC Pediatr. 2012;12:154.
9. Kundi M, Obermeier P, Helfert S, Oubari H, Fitzinger S, Yun JA, et al. The impact of the parent-physician relationship on parental vaccine safety perceptions. Curr Drug Saf. 2015;10(1):16-22.
10. Gust DA, Darling N, Kennedy A, Schwartz B. Parents with doubts about vaccines: which vaccines and reasons why. Pediatrics. 2008;122(4):718-25.
11. Jo DS, Kim JS. Perspectives on vaccine injury compensation program in Korea: the pediatricians' view. Clin Exp Vaccine Res. 2013;2(1):53-7.
12. Williams SE, Edwards KM, Baxter RP, LaRussa PS, Halsey NA, Dekker CL, et al. Comprehensive assessment of serious adverse events following immunization by health care providers. J Pediatr. 2013;162(6):1276-81, 81 e1.
13. WHO. Causality assessment of an adverse event following immunization (AEFI) - User manual for the revised WHO AEFI causality assessment classification. 2013. (Accesed Mai 15, 2015, at http://www.who.int/vaccine_safety/publications/gvs_aefi/en/).
14. Tafuri S, Gallone MS, Calabrese G, Germinario C. Adverse events following immunization: is this time for the use of WHO causality assessment? Expert Rev Vaccines. 2015;14(5):625-7.
15. Meranus D, Stergachis A, Arnold J, Duchin J. Assessing vaccine safety communication with healthcare providers in a large urban county. Pharmacoepidemiol Drug Saf. 2012;21(3):269-75.
16. CIOMS. Definitions and Applications of Terms for Vaccine Pharmacovigilance. 2012. (Accessed March 31, 2013, at http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf).
17. Graham JE, Borda-Rodriguez A, Huzair F, Zinck E. Capacity for a global vaccine safety system: the perspective of national regulatory authorities. Vaccine. 2012;30(33):4953-9.
18. MacDonald NE, Guichard S, Amarasinghe A, Balakrishnan MR, Inter-country SWP. Strengthening of causality assessment of adverse events following immunization in the WHO South East Asia and Western Pacific regions: Lessons from the 2014 SEAR inter-country workshop. Vaccine. 2015.

19. Zanoni G, Berra P, Lucchi I, Ferro A, O'Flanagan D, Levy-Bruhl D, et al. Vaccine adverse event monitoring systems across the European Union countries: time for unifying efforts. Vaccine. 2009;27(25-26):3376-84.
20. Tregoning JS, Schwarze J. Respiratory viral infections in infants: causes, clinical symptoms, virology, and immunology. Clin Microbiol Rev. 2010;23(1):74-98.
21. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis. 2009;9(5):291-300.
22. Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Madhi SA, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet. 2011;378(9807):1917-30.
23. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet. 2010;375(9725):1545-55.
24. Mantadakis E, Farmaki E, Thomaidis S, Tsalkidis A, Chatzimichael A. A case of immune thrombocytopenic purpura after influenza vaccination: consequence or coincidence? J Pediatr Hematol Oncol. 2010;32(6):e227-9.
25. Hehn J, Hartmann K, Brocker EB, Goebeler M. [Influenza vaccination and skin disease--coincidence or causal association?]. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology: JDDG. 2003;1(2):99-104.
26. Heininger U. Coincidence is not causality-a principle which needs regular rediscovery. Arch Dis Child. 2000;83(4):355.
27. Ruest A, Michaud S, Deslandes S, Frost EH. Comparison of the Directigen flu A+B test, the QuickVue influenza test, and clinical case definition to viral culture and reverse transcription-PCR for rapid diagnosis of influenza virus infection. J Clin Microbiol. 2003;41(8):3487-93.
28. Poehling KA, Zhu Y, Tang YW, Edwards K. Accuracy and impact of a point-of-care rapid influenza test in young children with respiratory illnesses. Arch Pediatr Adolesc Med. 2006;160(7):713-8.
29. Grijalva CG, Poehling KA, Edwards KM, Weinberg GA, Staat MA, Iwane MK, et al. Accuracy and interpretation of rapid influenza tests in children. Pediatrics. 2007;119(1):e6-11.
30. Dunn JJ, Gordon C, Kelley C, Carroll KC. Comparison of the Denka-Seiken INFLU A.B-Quick and BD Directigen Flu A+B kits with direct fluorescent-antibody staining and shell vial culture methods for rapid detection of influenza viruses. J Clin Microbiol. 2003;41(5):2180-3.
31. Uyeki TM, Prasad R, Vukotich C, Stebbins S, Rinaldo CR, Ferng YH, et al. Low sensitivity of rapid diagnostic test for influenza. Clin Infect Dis. 2009;48(9):e89-92.
32. Steininger C, Redlberger M, Graninger W, Kundi M, Popow-Kraupp T. Near-patient assays for diagnosis of influenza virus infection in adult patients. Clin Microbiol Infect. 2009;15(3):267-73.
33. Rath B, von Kleist M, Tief F, Karsch K, Tuerk E, Muehlhans S, et al. Virus load kinetics and resistance development during oseltamivir treatment in infants and children infected with Influenza A(H1N1) 2009 and Influenza B viruses. Pediatr Infect Dis. 2012;31(9):899-905.
34. Reiche J, Schweiger B. Genetic variability of group A human respiratory syncytial virus strains circulating in Germany from 1998 to 2007. J Clin Microbiol. 2009;47(6):1800-10.
35. Vandermeulen C, Roelants M, Theeten H, Van Damme P, Hoppenbrouwers K. Vaccination coverage and sociodemographic determinants of measles-mumps-rubella vaccination in three different age groups. Eur J Pediatr. 2008;167(10):1161-8.
36. CONSORT. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. 2010. (Accessed June 30, 2015, at http://www.consort-statement.org/downloads/consort-statement).

37. Crawford NW, Clothier H, Hodgson K, Selvaraj G, Easton ML, Buttery JP. Active surveillance for adverse events following immunization. Expert Rev Vaccines. 2014;13(2):265-76.
38. Regan AK, Blyth CC, Tracey L, Mak DB, Richmond PC, Effler PV. Comparison of text-messaging to voice telephone interviews for active surveillance of adverse events following immunisation. Vaccine. 2015.
39. Tamminga C, Kavanaugh M, Fedders C, Maiolatesi S, Abraham N, Bonhoeffer J, et al. A systematic review of safety data reporting in clinical trials of vaccines against malaria, tuberculosis, and human immunodeficiency virus. Vaccine. 2013;31(35):3628-35.
40. Asturias EJ, Contreras-Roldan IL, Ram M, Garcia-Melgar AJ, Morales-Oquendo V, Hartman K, et al. Post-authorization safety surveillance of a liquid pentavalent vaccine in Guatemalan children. Vaccine. 2013;31(49):5909-14.
41. Ali M, Rath B, Thiem VD. Vaccine safety monitoring systems in developing countries: an example of the Vietnam model. Curr Drug Saf. 2015;10(1):60-7.
42. Amarasinghe A, Black S, Bonhoeffer J, Carvalho SM, Dodoo A, Eskola J, et al. Effective vaccine safety systems in all countries: a challenge for more equitable access to immunization. Vaccine. 2013;31 Suppl 2:B108-14.
43. Kaddar M, Schmitt S, Makinen M, Milstien J. Global support for new vaccine implementation in middle-income countries. Vaccine. 2013;31 Suppl 2:B81-96.
44. Wilson K, Atkinson KM, Westeinde J. APPS for immunization- Leveraging mobile devices to place the individual at the center of care. Hum Vaccin Immunother. 2015:0.
45. Parrella A, Braunack-Mayer A, Gold M, Marshall H, Baghurst P. Healthcare providers' knowledge, experience and challenges of reporting adverse events following immunisation: a qualitative study. BMC Health Serv Res. 2013;13:313.
46. Banerjee AK, Okun S, Edwards IR, Wicks P, Smith MY, Mayall SJ, et al. Patient-Reported Outcome Measures in Safety Event Reporting: PROSPER Consortium guidance. Drug Saf. 2013;36(12):1129-49.
47. Williams SE, Klein NP, Halsey N, Dekker CL, Baxter RP, Marchant CD, et al. Overview of the Clinical Consult Case Review of adverse events following immunization: Clinical Immunization Safety Assessment (CISA) network 2004-2009. Vaccine. 2011;29(40):6920-7.
48. Mentzer D, Keller-Stanislawski, B. Daten zur Pharmakovigilanz von Impfstoffen aus dem Jahr 2011. Bulletin zur Arzneimittelsicherheit 1: 18-24. 2013.
49. Alicino C, Merlano C, Zappettini S, Schiaffino S, Della Luna G, Accardo C, et al. Routine surveillance of adverse events following immunization as an important tool to monitor vaccine safety. Hum Vaccin Immunother. 2015;11(1):91-4.
50. Zanoni G, Ferro A, Valsecchi M, Tridente G. The "Green Channel" of the Veneto region as a model for vaccine safety monitoring in Italy. Vaccine. 2005;23(17-18):2354-8.
51. Choe YJ, Bae GR. Management of vaccine safety in Korea. Clin Exp Vaccine Res. 2013;2(1):40-5.
52. InfoVac. InfoVac. 2014. (Accesed June 5, 2015 at http://www.infovac.ch/de/).
53. Olson LM, Inkelas M, Halfon N, Schuster MA, O'Connor KG, Mistry R. Overview of the content of health supervision for young children: reports from parents and pediatricians. Pediatrics. 2004;113(6 Suppl):1907-16.
54. Davis TC, Fredrickson DD, Arnold CL, Cross JT, Humiston SG, Green KW, et al. Childhood vaccine risk/benefit communication in private practice office settings: a national survey. Pediatrics. 2001;107(2):E17.
55. Parrella A, Gold M, Marshall H, Braunack-Mayer A, Baghurst P. Parental perspectives of vaccine safety and experience of adverse events following immunisation. Vaccine. 2013;31(16):2067-74.

56. Sarnquist C, Sawyer M, Calvin K, Mason W, Blumberg D, Luther J, et al. Communicating about vaccines and vaccine safety: what are medical residents learning and what do they want to learn? J Public Health Manag Pract. 2013;19(1):40-6.
57. Poland CM, Poland GA. Vaccine education spectrum disorder: the importance of incorporating psychological and cognitive models into vaccine education. Vaccine. 2011;29(37):6145-8.
58. Maurer W, Seeber L, Rundblad G, Kochhar S, Trusko B, Kisler B, et al. Standardization and simplification of vaccination records. Expert Rev Vaccines. 2014;13(4):545-59.
59. Davies EC, Chandler CI, Innocent SH, Kalumuna C, Terlouw DJ, Lalloo DG, et al. Designing adverse event forms for real-world reporting: participatory research in Uganda. PloS One. 2012;7(3):e32704.
60. WHO. Vaccine Safety Basics. 2013. (Accesed May 3, 2013 at http://www.vaccine-safety-training.org/).
61. Landry ML. Diagnostic tests for influenza infection. Curr Opin Pediatr. 2011;23(1):91-7.
62. Vashist SK, Mudanyali O, Schneider EM, Zengerle R, Ozcan A. Cellphone-based devices for bioanalytical sciences. Anal Bioanal Chem. 2014;406(14):3263-77.
63. Lewandrowski K, Tamerius J, Menegus M, Olivo PD, Lollar R, Lee-Lewandrowski E. Detection of influenza A and B viruses with the Sofia analyzer: a novel, rapid immunofluorescence-based in vitro diagnostic device. Am J Clin Pathol. 2013;139(5):684-9.
64. Lee CK, Cho CH, Woo MK, Nyeck AE, Lim CS, Kim WJ. Evaluation of Sofia fluorescent immunoassay analyzer for influenza A/B virus. J Clin Virol. 2012;55(3):239-43.
65. Leonardi GP, Wilson AM, Dauz M, Zuretti AR. Evaluation of respiratory syncytial virus (RSV) direct antigen detection assays for use in point-of-care testing. J Virol Methods. 2015;213:131-4.
66. Gomez S, Prieto C, Vera C, J RO, Folgueira L. Evaluation of a new rapid diagnostic test for the detection of influenza and RSV. Enferm Infecc Microbiol Clin. [Epub ahead of print]. June 29, 2015.
67. Kanwar N, Hassan F, Nguyen A, Selvarangan R. Head-to-head comparison of the diagnostic accuracies of BD Veritor System RSV and Quidel(R) Sofia(R) RSV FIA systems for respiratory syncytial virus (RSV) diagnosis. J Clin Virol. 2015;65:83-6.
68. FDA. Proposed Reclassification of the Rapid Influenza Detection Tests. 2013. (Accesed June 29, 2015 at http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-adcom/documents/document/ucm356185.pdf).
69. Moore C. Point-of-care tests for infection control: should rapid testing be in the laboratory or at the front line? J Hosp Infect. 2013;85(1):1-7.

Affidavit

I, Susann Mühlhans, certify under penalty of perjury by my own signature that I have submitted the thesis on the topic "Enhancing Vaccine Safety Monitoring and the Accurate Reporting and Differential Diagnosis of Adverse Events in Clinical Research and the Pediatric Acute Care Setting". 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

Detailed Declaration of Contribution

Susann Mühlhans had the following share in the following publication:

Publication 1:

Muehlhans S, Richard G, Ali M, Codarini G, Elemuwa C, Khamesipour A, Maurer W, Mworozi E, Kochhar S, Rundblad G, Vuitton D, Rath B. *Safety reporting in developing country vaccine clinical trials - A systematic review.* Vaccine. 2012.

Contribution 70%, contribution in detail:

Contribution on literature search, review and analysis of literature data and writing first draft of the manuscript, contribution to revisions of the manuscript during peer review.

Publication 2:

Muehlhans S, von Kleist M, Gretchukha T, Terhardt M, Fegeler U, Maurer W, Namazova-Baranova L, Gaedicke G, Baranov A, Rath B. *Awareness and Utilization of Reporting Pathways for Adverse Events Following Immunization: Online Survey Among Pediatricians in Russia and Germany.* Paediatr Drugs. 2014.

Contribution 80%, contribution in detail:

Translation of survey questionnaire into German, recruitment of survey participants, collection, ascertainment, collection and analysis of data and writing the first draft of the manuscript, contribution to revisions of the manuscript during peer review.

Publication 3:

Rath B, Tief F, Obermeier P, Tuerk E, Karsch K, **Muehlhans S**, Adamou E, Duwe S, Schweiger B. *Early Detection of Influenza A & B Infection in Infants and Children using Conventional and Fluorescence-based Rapid Testing.* J Clin Virol. 2012.

Contribution 15 %, contribution in detail:

Patient recruitment and performance of experiments.

Publication 4:

Tuttle RC, 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 a Novel Second-Generation Rapid RSV Test at the Point-of-Care.* Diagn Microbiol Infect Dis. 2015.

Contribution 10 %, contribution in detail:

Patient recruitment and performance of experiments.

Publication 5:

Rath B, **Muehlhans S**, Gaedicke G. *Teaching Vaccine Safety Communication to Medical Students and Health Professionals.* Curr Drug Saf. 2015.

Contribution 30 %, contribution in detail:

Contribution on literature search, review and analysis of literature data.

Signature, date and stamp of the supervising university teacher

_____

Signature of the doctoral candidate

_____

Print Copies of Selected Publications

Publication 1:

Muehlhans S, Richard G, Ali M, Codarini G, Elemuwa C, Khamesipour A, et al. *Safety reporting in developing country vaccine clinical trials-a systematic review.* Vaccine. 2012;30(22):3255-65.

Publication 2:

Muehlhans S, von Kleist M, Gretchukha T, Terhardt M, Fegeler U, Maurer W, et al. *Awareness and utilization of reporting pathways for adverse events following immunization: online survey among pediatricians in Russia and Germany.* Paediatr Drugs. 2014;16(4):321-30.

Publication 3:

Rath B, Tief F, Obermeier P, Tuerk E, Karsch K, **Muehlhans S**, et al. *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.

Publication 4:

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.

Publication 5:

Rath B, **Muehlhans S**, Gaedicke G. *Teaching vaccine safety communication to medical students and health professionals.* Curr Drug Saf. 2015;10(1):23-6.

Muehlhans S, Richard G, Ali M, Codarini G, Elemuwa C, Khamesipour A, et al. *Safety reporting in developing country vaccine clinical trials-a systematic review.* Vaccine. 2012 May 9;30(22):3255-65. doi: 10.1016/j.vaccine.2012.02.059. Epub 2012 Mar 7.

http://dx.doi.org/10.1016/j.vaccine.2012.02.059

Muehlhans S, von Kleist M, Gretchukha T, Terhardt M, Fegeler U, Maurer W, et al. *Awareness and utilization of reporting pathways for adverse events following immunization: online survey among pediatricians in Russia and Germany.* Paediatr Drugs. 2014 Aug;16(4):321-30. doi: 10.1007/s40272-014-0075-3.

http://dx.doi.org/10.1007/s40272-014-0075-3

Rath B, Tief F, Obermeier P, Tuerk E, Karsch K, **Muehlhans S**, et al. *Early detection of influenza A and B infection in infants and children using conventional and fluorescence-based rapid testing.* J Clin Virol. 2012 Dec;55(4):329-33. doi: 10.1016/j.jcv.2012.08.002. Epub 2012 Aug 24.

http://dx.doi.org/10.1016/j.jcv.2012.08.002

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 Mar;81(3):171-6. doi: 10.1016/j.diagmicrobio.2014.11.013. Epub 2014 Dec 3.

http://dx.doi.org/10.1016/j.diagmicrobio.2014.11.013

Rath B, **Muehlhans S**, Gaedicke G. *Teaching vaccine safety communication to medical students and health professionals.* Curr Drug Saf. 2015;10(1):23-6.

http://dx.doi.org/10.2174/1574886310011504071045 37

Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Publications

Muehlhans S, Richard G, Ali M, Codarini G, Elemuwa C, Khamesipour A, Maurer W, Mworozi E, Kochhar S, Rundblad G, Vuitton D, Rath B. *Safety reporting in developing country vaccine clinical trials-a systematic review.* Vaccine. 2012;30(22):3255-65.

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.

Rath B, von Kleist M, Tief F, Karsch K, Tuerk E, **Muehlhans S**, Louis F, Skopnik H, Schweiger B, Duwe S. *Virus load kinetics and resistance development during oseltamivir treatment in infants and children infected with Influenza A(H1N1) 2009 and Influenza B viruses.* Pediatr Infect Dis J. 2012;31(9):899-905.

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.

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.

Muehlhans S, von Kleist M, Gretchukha T, Terhardt M, Fegeler U, Maurer W, Namazova-Baranova L, Gaedicke G, Baranov A, Rath B. *Awareness and utilization of reporting pathways for adverse events following immunization: online survey among pediatricians in Russia and Germany.* Paediatr Drugs. 2014;16(4):321-30.

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.

Rath B, **Muehlhans S**, Gaedicke G. *Teaching vaccine safety communication to medical students and health professionals.* Curr Drug Saf. 2015;10(1):23-6.

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.

Presentations

Rath B, Tuerk E, Karsch K, Tief F, Verkin V, **Muehlhans S**, Schweiger B. *Simultaneous Influenza- and RSV Rapid Testing in Infants and Children with Influenza-Like Illness (Charité Influenza-Like Disease Cohort.* Poster Presentation, 4th ESWI Influenza Conference, Valetta, Malta: September 11-14, 2011.

Muehlhans S, Richard G, Khamesipour A, Maurer W, Mworozi E, Kochhar S, Vuitton D, Rath B. *Safety Reporting in Developing Country Vaccine Clinical Trials – A Systematic Review*. Poster Presentation, XVI Congress of Pediatricians of Russia, Moscow, Russian Federation: February 24-27, 2012.

Muehlhans S, Wiesenthal D, Terhardt M, Fegeler U, Gretchuka T, Galytskaya M, Gaedicke G, Baranova-Namazova L, Baranov A, Rath B. *Assessing Vaccine Safety Perceptions among Members of Pediatric Professional Associations – a Collaborative Study with the Union of Pediatricians of Russia and the German Professional Association of Pediatric and Adolescent Medicine Providers (BVKJ).* Panel Presentation, XVI Congress of Pediatricians of Russia, Moscow, Russian Federation: February 24-27, 2012.

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.

Rath B, von Kleist M, Tief F, Karsch K, Tuerk E, **Muehlhans S**, Louis F, Skopnik H, Schweiger B, Duwe S. *Shedding of resistant and susceptible influenza viruses in infants during oseltamivir treatment.* Poster Presentation, 3rd International Influenza Meeting, Muenster, Germany, September 2-4, 2012.

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.

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, Iguazu Falls, Brazil, May 4-8, 2014.

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 Fifth ESWI Influenza Conference, Riga, Latvia, September 14-17, 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.

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.

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.

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.

Acknowledgement

I would like to thank all of my colleagues in the Pediatric Infectious Disease Workgroup at Charité (PI: Dr. Barbara Rath), who made my dissertation possible. This has been a truly unforgettable experience for me. I would also like to thank our collaborative partners at the Robert Koch Institute and the international scientists, who have contributed to this work, either as collaborators or as peer reviewers.

First of all, I would like to express my deepest gratitude to my supervisor on-site Dr. Barbara Rath, for all the motivation, patience, as well as her knowledge and helpful advice throughout the successful course of this doctoral thesis. She sets high standards for her students and encourages and guides them to meet those standards. I thank her for her systematic guidance and effort she put into training me in the field of clinical research in pediatric infectious diseases and vaccines. Furthermore I would like to thank her for giving me the opportunity to attend a Pediatric Conference in Moscow to present my work, and for being available to me at any time when I had questions or concerns.

Besides my supervisor on-site, I would like to thank my overall thesis supervisor Prof. Dr. Gerhard Gaedicke for his insightful comments and advice, as well as for his encouragement until the completion of my thesis.

My sincere thanks go to my research team members, Franziska, Katharina, Lea, Xi, Patrick and Christian for the stimulating and constructive discussions we have shared, the sleepless nights we have spent working together, and - unforgotten - for all the enormous fun we have had in the past years.

I would like to thank Grit, Leonora and Stanley for their continuous care, energy, encouragement, and precious friendship through both good and bad times, no matter whether near or far.

Finally, I take this opportunity to express the profound gratitude to my beloved parents Sylka and Falk, my sister Annett and nephew Max who have been a constant source of love, concern, support and strength in my life.