Dissertation

Epidemiological aspects of selected vaccine preventable infectious diseases: measles, influenza and tick-borne encephalitis

submitted by

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Statutory Declaration

I hereby declare that this thesis is my original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz”.

Benno Kohlmaier

Graz, 14.05.2022

Disclosures

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Vorwort (Deutsch)

Diese kumulative Dissertation entstand im Rahmen meiner ärztlichen und wissenschaftlichen Tätigkeit im Bereich der pädiatrischen Infektiologie. In dieser Zeit konnte ich neben der Betreuung des Horizon2020 EU-Projektes PERFORM (https://www.perform2020.org/) wertvolle Erfahrungen in verschiedensten Bereichen der Infektiologie und folglich auch Präventionsmedizin erlangen. Die hieraus resultierende Dissertationsarbeit berichtet über impfpräventable Erkrankungen, einem wichtigen Teilbereich der Infektiologie. Die drei impfpräventablen Erkrankungen, Masern, Influenza und FSME, die in dieser Arbeit genannt werden, benötigen einer ständigen Beobachtung um einerseits die Effekte der Impfungen zu erfassen, um zu analysieren ob die Impfprogramme adaptiert werden müssen und andererseits um durch die Dokumentation der Krankheitsbelastung Argumente für die Impfungen der Öffentlichkeit aufzeigen zu können.

Aufgrund der COVID-19 Pandemie ist dieses Thema höchst aktuell und erfährt eine große Bedeutungszunahme. In den letzten Monaten konnten wir durch die Maßnahmen zur Eindämmung der Pandemie eine deutliche Verhaltensänderung der Bevölkerung beobachten. „Social distancing“, Tragen von Nasen-Mund-Masken, Desinfektionsmaßnahmen und generell eine erhöhte „Awareness“ für mögliche Übertragung von Infektionskrankheiten haben sich stark in den Inzidenzzahlen pädiatrischer Infektionserkrankungen niedergeschlagen. Hier zeigte sich insbesondere die Bedeutung des Transmissionswegs von Infektionskrankheiten.
Während die Influenzasaison 2019/20 in der Kalenderwoche 6 mit 2.314 Influenza-like-illness (ILI) Erkrankungen pro 100.000 Einwohnern ihren Höhepunkt hatte, waren es in der folgenden Saison mit 1.013 Erkrankungen pro 100.000 Einwohnern deutlich weniger. Zusätzlich war die Zahl der laborbestätigten Influenza-Fälle derart niedrig, dass keine Influenzaepidemie ausgerufen wurde. Auch die Fälle der gemeldeten Masernerkrankungen sanken von 151 Fällen im Jahr 2019 auf 25 Fälle im Jahr 2020. Bei Vektor-übertragenen Erkrankungen wie Frühsommer-Meningoenzephalitis (FSME) konnte naturgemäß hingegen kein relevanter Rückgang beobachtet werden. Hier zeigte sich sogar eine Zunahme von 108 Fällen im Jahr 2019 auf 215 Fälle im Jahr 2020.

Es steht fest, dass Infektionserkrankungen, selbst wenn diese bereits seit Jahrzehnten bekannt sind, einer fortwährenden wissenschaftlichen Beobachtung, Analyse und Bewertung erfordern, um sowohl bestehende Strategien der Krankheitsprävention zu aktualisieren als auch neue zu etablieren.

In diesem Zusammenhang freut mich besonders die Tatsache, dass die Publikation „A severe influenza season in Austria and its impact on the paediatric population: mortality and hospital admission rates, november 2017 - march 2018“ von der Österreichischen Bundesregierung als Entscheidungsgrundlage genommen wurde, um die saisonale Influenzaimpfung bundesweit in das kostenlose Impfprogramm für alle Kinder und Jugendliche aufzunehmen.

Ich hoffe mit dieser Dissertation einen weiteren Beitrag zur wissenschaftlichen Erkenntnis über impfpräventable Erkrankungen leisten zu können.

Graz, am 14.05.2022

Prologue (English)

This cumulative dissertation was written during my employment as medical doctor and clinical researcher in paediatric infectious diseases. Besides working as a study coordinator for PERFORM (https://www.perform2020.org/), a Horizon2020 EU-project, I could learn about various aspects of infectiology and preventive medicine. This resulted in three publications about vaccine preventable disease, as an important part of infectiology. In particular, I report about various aspects of measles, influenza and tick-borne encephalitis. Continuous monitoring and surveillance of these diseases is necessary to observe effects of vaccination, to analyse if vaccination programmes need adjustment and to document the burden of disease as an impulse to support future vaccinations recommendations.

Caused by the COVID-19 pandemic these topics are highly up-to-date. During the previous months, the behaviour of most people changed. Social distancing, facemasks, disinfection measures and a generally raised awareness towards disease transmission was initiated. The restrictions limited further COVID-19 transmission but also transmission of other infections with a drastic change of incidence numbers of paediatric infectious diseases. This showed the importance of transmission routes of infectious diseases.

In 2020, at calendar week 6, the influenza season 2019/20 had its peak with 2,314 Influenza-like-illness (ILI) per 100,000 inhabitants, while the following season was much milder with 1,013 ILI per 100,000 inhabitants. During this season, the number of laboratory confirmed influenza cases was even below the threshold to proclaim an influenza epidemic. A similar trend was seen in reported measles cases, which declined form 151 cases in 2019 to 25 cases in 2020. Meanwhile, the incidence of tick-borne encephalitis raised from 108 cases in 2019 to 215 cases in 2020.

It is important to notice that infectious diseases need continuous observation, analysis and evaluation, to renew existing and establish new strategies of disease prevention, even when the disease is known for a long time.

Encouragingly, the publication “A severe influenza season in Austria and its impact on the paediatric population: mortality and hospital admission rates, november 2017 - march 2018“ was cited by the Austrian Government when it was decided to provide the annual influenza vaccination for all children and adolescents free of charge.

In conclusion, I hope that this dissertation thesis contributes to further scientific insights and understanding about vaccine preventable diseases.

Graz, 14th May 2022

Danksagungen (Deutsch)

Ich möchte mich sehr herzlich bei allen Mitarbeiter*innen der Univ.-Klinik für Kinder- und Jugendheilkunde bedanken. Dank Ihnen konnte ich im Laufe der letzten Jahre mein Wissen vertiefen und mich in das Abenteuer pädiatrische Infektiologie stürzen. Besonderer Dank gilt meinen Betreuern Prof. Dr. Werner Zenz für seinen Vertrauensvorschuss und wissenschaftliche Begleitung, Nina Schweintzger, MSc. PhD., für ihre wertvollen Ideen und Priv.-Doz. Dr. Alexander Pichler für seine Kooperation bei mehreren wissenschaftlichen Projekten und seiner wertvollen Unterstützung sowohl in klinischen wie auch bei vielen wissenschaftlichen Fragen. Mein weiterer Dank gilt allen Mitgliedern der internationalen Studiengruppe „EU-TICK-BO“ sowie der nationalen Studiengruppe „Austrian Paediatric Influenza Network“ ohne deren Hilfe die Aufzeichnung einer relevanten internationalen bzw. österreichweiten Patient*Innenkohorte unmöglich gewesen wäre. Zuletzt möchte ich mich bei meiner Frau Anna und meinem Sohn Junes für ihre liebevolle Geduld und großartige Unterstützung bedanken.

Acknowledgement (English)

I want to thank all employees of the Department of Children and Adolescent Medicine. Thanks to your support, I was able to engage with the adventure of paediatric infectiology. My special thanks goes to my supervisor Prof. Werner Zenz for his mentoring and trust, to Nina Schweintzger, Msc. PhD., for her helpful ideas and to Priv.Doz. Dr. Alexander Pichler for his support and cooperation in several scientific projects and clinical issues. Further, my thanks goes to all members of the international study group “EU-TICK-BO” and the national study group “Austrian Paediatric Influenza Network”. Without their help, it would have been impossible to collect highly relevant international and national patient cohorts. Finally, my special thanks goes to my wife Anna and my son Junes for their patience and great support.

Abstract (Deutsch)

Die ersten modernen Impfungen wurden Ende des 18. Jahrhunderts entwickelt. Seither schrieben Impfungen Medizingeschichte und veränderten unser Verständnis von Infektionskrankheiten und deren Prävention. Innerhalb der folgenden Jahrhunderte wurden Impfungen gegen zahlreiche virale und bakterielle Erkrankungen etabliert und retteten so das Leben von Millionen von Menschen. Gemeinsam mit der Einführung von modernen Hygienemaßnahmen konnten Meilensteine der Medizin erreicht werden. Hierauf zeigten sich fallende Inzidenzzahlen vieler Infektionserkrankungen, die klassisch als Kinderkrankheiten betrachtet wurden, woraufhin es im weiteren zu einem drastischen Rückgang der Kindersterblichkeit kam. 1980 gelang es sogar erstmals eine durch Impfung verhinderbare Erkrankung, die Pocken, weltweit auszurotten.

Heute schreitet die Entwicklung von Impfstoffen weiter voran und wir begegnen neuen Herausforderungen, wie der globalen COVID-19 Pandemie, sowie neuen Möglichkeiten und Zielen, wie eine globale Maserneradikation. Zeitgleich ist es wichtig, Infektionserkrankungen, gegen die es bereits eine Impfung gibt, weiter zu beobachten und Veränderungen ihrer klinischen und epidemiologischen Bereiche zu erforschen. Diese kumulative Dissertationsarbeit vereint nun drei Publikationen über impfpräventable Erkrankungen und deren klinische und epidemiologische Aspekte.

Die erste hier vorgestellte Publikation berichtet über einen Masernausbruch an der Univ.-Klinik für Kinder- und Jugendheilkunde der Medizinischen Universität Graz mit 13 Erkrankungsfällen im Februar 2017. Masern, eine klassische Kinderkrankheit, zeigte sich in den letzten Jahrzehnten deutlich seltener und viele, vor allem junge Kinderärzte, kennen Masern nur noch aus dem Lehrbuch. Im Rahmen des Masernausbruchs 2017 wurde nur 1 von 8 Masernpatient*innen ohne anamnestischen Hinweis auf Masernkontakt bei der Erstvorstellung erkannt. Eine detaillierte Beschreibung der klinischen Präsentation und mögliche Gründe für Fehlinterpretationen werden erörtert.

Die zweite Publikation beschreibt die Influenzasaison 2017/18 bei Kindern und Jugendlichen in Österreich. Zum ersten Mal wurde hierfür eine aktive Surveillance verwendet, womit eine deutlich höhere Hospitalisierungsrate und Sterblichkeit im Vergleich zu den Vorjahren gezeigt werden konnte.

Im Rahmen der dritten Publikation wird eine Kohorte mit 555 Fällen von Frühsommer-Meningoenzephalitis (FSME) beschrieben. Wir berichten detailliert über den klinischen Verlauf der Patient*innen, welche im Rahmen der internationalen Studie EU-TICK-BO (European genetics study of tick-borne encephalitis) rekrutiert wurden. Hierfür wurde ein universeller Patientendokumentationsbogen (Case Record Form, CRF) entworfen, um eine einheitliche Auswertung der von verschiedenen Zentren erhobenen Daten zu ermöglichen.

Zusammengefasst, beschäftigt sich diese kumulative Dissertation mit der klinischen Charakteristik, der Übertragung, den diagnostischen Herausforderungen und der Surveillance von Masern, Influenza und FSME.

Abstract (English)

Since the introduction of the first vaccine in the late 18th century, our understanding of infectious diseases and prevention strategies has changed dramatically. Within the following centuries several vaccinations against viral and bacterial infections had been developed and saved millions of lives. Together with the growing understanding of hygiene, vaccinations dramatically reduced infant death rates and incidence rates of childhood diseases such as measles. As a consequence of the vaccination against smallpox, the World Health Assembly declared smallpox eradicated in 1980.

Today, the benefit of vaccinations still progresses and we face new challenges - such as the COVID-pandemic – and opportunities, such as the globally elimination of big killers like measles. While we see a steady rise of development and approval of new vaccines, it remains important to keep an eye on diseases where vaccines are already available. After the introduction of vaccinations, we observed a drastic reduction of incidence rates and changes of several clinical aspects. This thesis focuses on epidemiological aspects of three selected vaccine preventable diseases.

The first publication reports about measles recognition during an outbreak with thirteen confirmed measles patients in February 2017. Measles, a disease which is known to each paediatrician has become rare and many, especially young, clinicians have never seen a measles patient themselves. Of eight cases with no known epidemiological link, only one was diagnosed at the initial presentation; four were recognised with delay and three only retrospectively. A detailed analysis of cases is shown and possible reasons of non-recognition have been identified.

The second publication describes paediatric influenza during the season 2017/18. It was the first active surveillance of paediatric influenza in Austria, which revealed much higher numbers of hospitalisation and fatal cases than in previous years, reported by ICD-10 codes.

The third publication is a detailed clinical description of patients with tick-borne encephalitis (TBE) across several endemic European countries. It is the first international multicentre study using a common case record form (CRF) and confirms that TBE is still a dangerous disease with high rates of patients with incomplete recovery at discharge.

In summary, this cumulative thesis gives an insight into three vaccine preventable disease, measles, influenza and tick-borne encephalitis with focus on clinical characteristics, transmission of disease, diagnostic challenges and disease surveillance.

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1 Introduction

1.1 Measles

1.1.1 Measles virus infection

Measles is caused by a single-stranded RNA virus of the genus Morbillivirus and the family Paramyxoviridae. The disease presents as a febrile illness with a typical maculopapular rash. Due to the relatively high rate of complications especially in immunocompromised or undernourished persons, measles is a major cause of mortality in children worldwide and remains a leading cause of vaccine-preventable illness and death with an estimated 100,000 deaths each year (1). The burden of disease dropped rapidly after the introduction of an immunization against measles in the 1960s. In the USA and many European countries measles is no longer endemic and sporadic outbreaks are caused by transmission from imported cases (2).
Humans are the only natural host of the virus and the World Health Organisation (WHO) aimed to ultimately eliminate measles, a goal that has not been reached so far (3).

1.1.2 Clinical characteristics of measles

The clinical course of measles has been studied in detail and is described in various medical text books and publications. The incubation time usually is 8-12 days after exposure and is clinically inapparent (4). The prodromal phase is characterized by fever, rhinitis, and coughing and is also called ‘catarrhal phase’. It is further characterized by pronounced coughing and bilateral conjunctivitis and there may be eye pain and sensitivity to light (5,6). At the height of the fever a rash develops at the face and distributes across the whole body, including the palms and soles (7). This phase is called the ‘rash phase’. The rash is erythematous and maculopapular, and not itchy (8). In the recovery phase the rash fades in the inverse direction as it appeared and ends approximately 10-14 days after the beginning of the rash (7). Further, 1-2 days before the rash begins white spots can be seen on the buccal mucosa and are called ‘Koplik’s spots’ (9). This is considered pathognomonic for measles (6).

Complications are otitis media (7–9%), pneumonia (1–6%), diarrhoea (8%), post-infectious encephalitis (1 per 1000 to 2000 cases). A most dramatic complication is subacute sclerosing panencephalitis (SSPE), with appears month to years after a measles infection with a 100% lethality. Reported SSPE incidence varies greatly and is considered to be approximately 4–11 cases per 100 000 measles cases with highest risk in infants (10).
Mortality is mainly caused by bacterial co-infections and case fatality is 1-3 per 1000 cases with highest rates among children younger than 5 years, immunocompromised and undernourished persons with vitamin A deficiencies as seen in developing countries (11).

1.1.3 Transmission and prevention of measles

Measles is one of the most contagious infectious diseases worldwide with an infectivity of almost 100% in susceptible individuals (12). The basic reproduction number in measles (R0), which is defined as the average number of secondary cases of an infectious disease arising from an index case in a susceptible population, is estimated 12-18 with wide ranges according to different covariates such as pre-vaccine and vaccine-era, WHO regions and population density (13).
Measles are transmitted by droplets or airborne transmission (14,15). Experimental studies showed a persistence of measles virus particles in air for several hours according to room temperature and humidity, with longer survival of the virus in dry rooms, which might explain higher incidence rates during winter (16). Accordingly, a room should be considered infectious up to 2 hours after a measles patient has left and preventive measures including surface disinfection and air ventilation should be performed.

While there is no specific treatment for infected persons, a post-exposure prophylaxis (PEP) can be given in contacts. Unvaccinated persons older than 6 months should be vaccinated up to 72 hours after the contact. Persons younger than 6 months should receive passive prophylaxis with immunoglobulins. Further, infants can be tested for protective maternal antibodies if results are available within a reasonable time (17,18).

The best preventive measurement is measles vaccination, which is generally recommended in Austria and should be applied from 9 months age on. During measles

outbreaks the first dose can be given at 6 months of age. Further, natural immunity in infants might be provided by maternal antibodies but protection rates vary greatly and are reported to wean at the age of 2-4 months (19).

In Austria, measles vaccination is free of charge for all children. Complete immunization rates vary according to age with more than 95% in children 6-18 years old and 82-88% in children 2-5 years old. Still, recurring measles outbreaks in Austria are observed with 151 cases in 2019 (20).

1.1.4 Diagnosis of measles

Measles can be difficult to distinguish from other febrile illnesses with rash, and infections with rubella, parvovirus B19, human herpes virus type 6 (HHV-6) and dengue can easily be mistaken for measles (21,22). Therefore, measles should be considered in all persons with fever and maculopapular rash, accompanied by cough, coryza and conjunctivitis.

According to the European Disease and Control (ECDC) case definitions clinical criteria include fever, maculo-papular rash and at least one of the following symptoms: cough, coryza and conjunctivitis. Laboratory criteria include at least one of the following: isolation of measles virus, detection of measles specific nucleic acid in clinical specimen, measles specific antibodies in serum or saliva and detection of measles virus antigen by Direct Immunofluorescence Assay (DFA) in a clinical specimen using measles specific monoclonal antibodies. Cases can be categorized as possible, probable and confirmed cases. Possible cases are persons meeting the clinical criteria, probable cases have an additional epidemiological link and proven cases additionally meet the laboratory criteria (23).

Today, testing for measles specific IgM is valid to prove measles infection as previous studies showed high sensibility and specificity of measles specific antibody detection with ELISA (24). Detection of measles RNA by real-time-PCR is possible as late as 10-14 days after rash onset and has a high sensitivity. It is a useful method to identify virus strains and uncover the chain of transmission (25).

1.1.5 Diagnostic challenges of measles

Fever and maculopapular rash are common symptoms and might be caused by various conditions, not only measles. Several other viral infections are accompanied by maculopapular rash including rubella, scarlet fever, roseola, infectious mononucleosis and rickettsia, enteroviral, and adenoviral infections. Fever and rash might also be caused by inflammatory syndromes such as Kawasaki syndrome or systemic juvenile idiopathic arthritis. The specific distribution and pattern of appearance of rash in measles patents helps distinguishing them from other aetiologies (6,26). Personal experience is helpful, but measles has become rare and sometimes young clinicians have never seen measles patients themselves (27).

Modified measles, characterized by less intense symptoms and a milder rash, are seen in patients with some sort of passive immunoglobulin exposure either in infants with maternal antibodies or in immunocompromised patients after admittance of immunoglobulins. Symptoms are variable and some common features such as prodromal phase, conjunctivitis, kolpik spots and even rash might be missing (28). Observations suggest a decreased risk of transmission in persons with modified measles in vaccinated persons (29).

Measles infections in vaccinated persons are rare and therefore, diagnosis might be challenging, because clinicians will tend to exclude measles as differential diagnosis in vaccinated persons. Health-care workers seem to be at higher risk for break-through infections, but transmission from persons with break-through infections seems to be rare (30).

1.1.6 Surveillance of measles outbreaks

Global measles eradication is a long-standing objective from public health experts (31). After the successful eradication of measles in Cuba with the last reported measles case in July 1993, WHO established the goal of global measles eradication (32). In order to achieve that vaccination strategies were updated and disease surveillance was extended. From 2000–2016, annual reported measles incidence decreased by 87%, from 145 to 19 cases per million persons, annual estimated measles deaths decreased by 84% (33).

In 2000, regional measles surveillance data in America reported effective interrupting of transmissions and absence of measles virus circulation in most parts of America and measles were declared eliminated from the United States of America, after robust surveillance did not detect a case for more than a year (34,35). Contrary, in many European countries measles outbreaks remained endemic. In 2018, measles were considered endemic in Belgium, Bosnia and Herzegovina, France, Georgia, Germany, Italy, Romania, the Russian Federation, Serbia, and the Ukraine (36). The cause of the still high measles incidences are low vaccination rates. While a vaccination coverage of more than 95% was shown to provide herd-immunity, several European countries couldn't reach this coverage. Only five EU/EEA countries (Hungary, Malta, Portugal, Slovakia and Sweden) reported at least 95% vaccination coverage for both the first and second doses in 2018 (37).

To observe the effects of vaccination programmes, a detailed measles surveillance is needed. Güris et al. described measles surveillance in the USA as follows:

"In the United States the measles surveillance system is geared towards detection of measles virus transmission, rapid discovery of measles outbreaks to facilitate outbreak control, and identification of risk factors for measles. The surveillance system is a passive reporting system that, when activated by a reported case of suspected measles, triggers a search for additional cases around the reported case. Cases are reported by health care providers or from schools and day care centers. The sensitivity of the system is increased through reporting and investigation of all suspected measles cases by means of an inclusive case definition (generalized maculopapular rash and fever), and the specificity is increased through laboratory testing for measles of all suspected cases" (38).

Measles surveillance in Austria is similar to the system in the USA. Reporting of suspected measles is mandatory and contacts are traced by health authorities. Information about measles activity in Austria, reports on vaccination rates and instructions for outbreak management are available on public healthcare websites (39).

1.2 Influenza

1.2.1 Influenza virus infection

Influenza is a viral disease transmitted by influenza virus which is a single-stranded RNA virus of the genus Orthomyxoviridae. Different subtypes include influenza A, B, C and D with A and B being the main players in global influence pandemics (6). Influenza occurs in outbreaks worldwide mainly during the winter period, is associated with 5 million hospitalizations per year and is a leading cause of cardiopulmonary morbidity and mortality worldwide (40,41). For the year 2017, 290 000-650 000 influenza-associated deaths from respiratory causes alone were estimated, and a 2019 study estimated 99 000-200 000 deaths from lower respiratory tract infections directly caused by influenza . (21,42). Young children below 10 years and aged adults older than 65 are at greatest risk for hospitalisation due to severe disease, with a tendency of males suffering more in these age groups. In the interim age groups females of reproductive ages (15–49 years) experience a worse outcome than their male counterparts (43).

Due to variations in circulating viral strains an annual influenza vaccination is provided each year according to World Health Organisation (WHO) recommendations. According to observations of Center of Disease Control (CDC) vaccine effectiveness ranges between 19-60% during the seasons 2010-2011 to 2019-2020 (44). Vaccination rates vary between countries and in Austria vaccination rate against influenza is about 8% and is among the lowest worldwide. This was proposed as vaccination paradox, since the vaccination rate of TBE (82%) is among the highest worldwide (45).

1.2.2 Clinical characteristics of influenza

Influenza is an acute respiratory disease. The incubation time is relatively short with 1-4 days (95% CI 1-3–1-55) for influenza A and 0-6 days (95% CI 0-5–0-6) for influenza B (46). It is characterized by a sudden onset of high fever, coryza, cough, headache, prostration, malaise, and inflammation of the upper respiratory tract and trachea (47). Both, in influenza A and B symptoms are similar and subtypes cannot be distinguished clinically (48).

The duration of the disease differs among age groups and observed nationality. In 0–14 years, 15–64 years and 65+ years it is 7.4 days, 8.7 and 10.5 days in France, and 6.3, 8.2 and 9.2 days in Turkey (49). Because of its typical characteristics of an acute respiratory disease with overlapping symptoms of many other infections a definitive diagnosis cannot be made on a sole clinical presentation.

Several complications in patients with influenza infection have been reported. Bacterial co-infections with Streptococcus pneumoniae as most common isolated pathogen, result in high mortality rates (50). General influenza mortality rates are variable and influenced by viral strains, patients age and comorbidities and annual death rates are estimated as excess mortality (also see chapter 1.2.6 - influenza surveillance).

1.2.3 Transmission and prevention of influenza

Influenza is an infection of the respiratory tract and the virus can be transmitted through sneezing and coughing. Influenza virus spreads by inhalation of virus-loaded droplets, by direct contact such as hand shaking and indirect contact by contaminated surfaces (51). Large epidemiological observations suggest that most influenza transmissions occur at close range, mostly by large droplets or direct contact e.g. hand shaking, while transmission by aerosol is also possible but seems to be less important (52,53). Surfaces as possible source of transmission have also been identified and the mechanism of transmission here might be transocular entry (54).

The best way to prevent infection with influenza is vaccination. Besides that, other recommendations are available, which include avoiding close contacts, staying home when being sick, cover mouth and nose, hand hygiene, avoid touching eyes and nose or mouth and other habits such as cleaning of surfaces (55).

Hand hygiene and facemasks were intensively investigated and show a high protection rate in hospital nosocomial transmission, with less effect on household transmissions (56,57). The universal wearing of face masks in all hospital areas during the COVID-19 pandemic further illustrates the effectiveness of preventive measures by absences of influenza and respiratory syncytial virus (RSV) nosocomial infections in several hospitals in the northern hemisphere (58).

Specific viral treatment is available. Neuraminidase inhibitors (e.g. Oseltamivir) are among the most recommended pharmacological treatments. The benefit of the treatment is higher when initiated promptly as the duration of symptoms is shortened. While the benefit for immunocompetent persons is controversially discussed, antiviral treatment should be given to patients at risk for complications. This includes patients with coexisting medical conditions e.g. asthma, chronic kidney disease, immunosuppression, as well as special groups e.g. patients older than 65 years, pregnant women or children younger than 2 years (59).

1.2.4 Diagnosis of influenza

ECDC case definition for Influenza includes the following clinical criteria: influenza-like illness (ILI) with sudden onset of symptoms, fever, malaise, headache, myalgia; and acute respiratory infection (ARI) with sudden onset of symptoms, cough, sore throat, shortness of breath. Laboratory criteria include isolation of virus, detection of virus nucleic acid, detection of Influenza antigen or Influenza specific antibody response. Various combinations result in either a possible case (only clinical criteria), a probable (clinical criteria with epidemiological link) or a confirmed case (clinical criteria and laboratory criteria) (23). Most cases are seasonal during the winter period and patients treated in the outpatient setting are diagnosed solely based on clinical criteria. Several pathogens are known to cause symptoms similar to Influenza such as Rhinovirus, RSV, human metapneumovirus (hMPV) and mycoplasma bacteria. Therefore, a laboratory diagnostic is needed to confirm the diagnosis. This is advised in the hospital setting in patients with severe disease that might benefit from antiviral treatment. Rapid viral antigen tests are broadly available and cheap, have a relatively low sensitivity (67-71% for Influenza A and 30% for Influenza B) and high specificity of 99-100% (60). Detection of virus nucleic acid is done using polymerase chain reaction (PCR). Today, Rapid Point-of-care (POC) PCR-testing has a growing popularity especially in urgent care centres with >95% sensitivity and specificity. The use of POC-PCR testing improved antiviral prescribing practices and likely reduces antibiotic prescription rates compared to rapid antigen testing (61).

1.2.5 Diagnostic challenges of influenza

Diagnosis of Influenza is complicated by unspecific symptoms. Most symptoms of influenza-like-illness (ILI) and acute respiratory tract infections (ARI) are similar to other viral respiratory tract infections (RSV, rhinovirus, adenovirus, parainfluenza viruses and human coronaviruses) (62). A case report also describes Dengue as possible differential diagnosis of Influenza, illustrating the wide range of possible differential diagnosis (63). The seasonal appearance of Influenza might be a helpful hint, but also most other respiratory viruses show a seasonal appearance during the winter period (64).
In late 2019 the novel virus SARS-CoV2 causing the COVID-19 pandemic appeared with further overlap of clinical symptoms (65). COVID-19 as potential differential diagnosis is not discussed in the thesis as all included observations were finished before the first description of the disease.

1.2.6 Surveillance of influenza infections

Seasonal influenza epidemics have a high impact on general mortality which can be observed as excess mortality. Long-time observations from Germany show variable excess mortality with average seasonal excess mortality estimates of 16.1 and 17.4 deaths per 100,000 population for the period 1985-1995 and 1991-2001, respectively. Seasonal estimates ranged between 2.2 and 44.2 excess deaths per 100,000 population, showing a broad annual variability (66).

To observe the effect of seasonal influenza epidemics, surveillance has been well established in most national health organisations around the world. The World Health Organisation (WHO) has a global Influenza programme and provides member states with strategic guidance, technical support and coordination of activities essential to make their health systems better prepared against influenza threats to populations and individuals (*https://www.who.int/health-topics/influenza-seasonal*). In 2007 the 'Pandemic Influenza Preparedness (PIP) Framework' was initiated. It brings together member states, industry, other stakeholders and WHO to implement a global approach to pandemic influenza

preparedness and response. Its key goal is a rapid identification and risk assessment of new influenza viral strains with pandemic potential and it ensures that at least 10% of the global production of pandemic influenza vaccines will be supplied to WHO (67).

The ECDC provides information about Influenza activities and gives weekly influenza updates as a joint project with the WHO available at *https://www.ecdc.europa.eu/en/seasonal-influenza/surveillance-and-disease-data/flu-news-europe*.
In Austria information about the current Influenza activity is provided by the AGES (Agentur für Gesundheit und Ernährungssicherheit GmbH) and "Projekt Diagnostisches Influenzanetzwerk Österreich" (DINÖ) by the Medical University of Vienna.

1.3 Tick-borne encephalitis (TBE)

1.3.1 TBE virus infection

Tick-borne encephalitis is a viral disease transmitted by the tick-borne encephalitis virus (TBEV), a member of the genus flavivirus, family Flaviviridae, which is an enveloped RNA virus (68). TBE-virus is transmitted by Ixodes species ticks and is endemic in several regions in Western Europe and Asia (69). TBE-virus is subdivided into three main subtypes—the European (TBEV-Eu), the Far-Eastern (TBEV-FE), and the Siberian (TBEV-Sib) (70). Here we focus on the European subtype. TBE was first described in Austria in 1931.The first vaccine was introduced in 1976 (FSME-Immun, Immuno AG) in Austria, which after implementation in the national vaccination programme, governmental advertisement and broad acceptance in the population led to a substantial decrease of cases (71).

1.3.2 Clinical characteristics of TBE

Incubation time is 8 days (range from 4-28 days) after a tick bite with a typically biphasic course of disease. The first phase that lasts for 5 days (range 2-10 days) is characterised by fever, general unwell-being and headache. After a symptom-free interval of 7 days (range 1-21 days) a second phase follows which is characterised by neurological symptoms ranging from mild meningitis to severe encephalitis with or without myelitis and spinal paralysis (69,72). Symptoms most commonly include headache, altered consciousness, seizures, ataxia, tremor, spinal and cranial nerve palsy (73–75). A preference of the TBE virus for the anterior horn of the cervical spinal cord resulting in flaccid paresis of extremities is seen in up to 10% of patients (76). The course of disease can be severe with need for intensive care treatment (7%) and mechanical ventilation (1%) (76). Incomplete recovery at time of discharge is often reported and ranges from headache and concentration difficulties to lasting paresis of extremities with low recovery rates leading to significant sequelae after TBE (77,78). Mortality differs among various reports and ranges from 0 to 6.3% (74,79–81).

1.3.3 Transmission and prevention of TBE

TBEV-Eu is transmitted by *Ixodes ricinus*, which is common in Central and Eastern Europe and can be found on birds and rodents in forest environment (82). TBEV is transmitted from the saliva of an infected tick within minutes of the tick-bite and early removal of ticks does not necessarily prevent infection (83).

Due to the natural reproductive circle of ticks seasonal patterns of TBEV-infections are seen. Tick bites start in spring at temperatures around 6°C and last until November. In central Europe two peaks can be seen in early and late summer, while in northern Europe one peak is described during July and August. Incidence is strongly influenced by human behaviour and leisure activities during summer months lead to higher rates of tick bites (84).

Unpasteurized milk is a further route of transmission, which was confirmed by TBEV positive RNA in the source animal's serum and milk and several outbreak reports (85,86).

Also, a case report was published describing a laboratory acquired transmission of TBE (87).

The best preventive measure of TBE is vaccination. Until the late 1990s, a post exposure prophylaxis using immunoglobulins was common, but is no longer used today. Immunoglobulins were administered to unvaccinated persons, but passive immunisation was blamed for anti-body enhancement in children and therefore discontinued (88). Until today, this hypothesis was not confirmed and in mouse models such a phenomenon could not be observed (89,90).

Post-exposure prophylaxis with vaccination is not recommended in unvaccinated persons, since two doses of vaccination are needed to establish a sufficient antibody load to prevent infection. For persons with a history of one dose of vaccine at least 15 days before the tick-bite and clinical consultation shorter than 48 hours after the bite, an immediate vaccination is recommended (17).

1.3.4 Diagnosis of TBE

ECDC case definition for TBE includes the following clinical criteria: Any person with symptoms of inflammation of the CNS. Laboratory criteria includes at least one of the following five: TBE specific IgM AND IgG antibodies in blood, TBE specific IgM antibodies in CSF, Seroconversion or four-fold increase of TBE-specific antibodies in paired serum samples, detection of TBE viral nucleic acid in a clinical specimen, isolation of TBE virus from clinical specimen. Patients are categorized into probable cases (persons meeting the clinical criteria and detection of TBE-specific IgM-antibodies in a unique serum sample) and definitive cases (meeting the clinical and laboratory criteria) (23).

1.3.5 Diagnostic challenges of TBE

TBE must be considered as a possible differential diagnosis in all patients with signs of meningitis and encephalitis during spring to autumn living in a TBE endemic area. A reported tick-bite is a valuable hint but remains unnoticed in about 1/3 of cases (91). Higher risks of infections are seen in persons with recreational or occupational exposure

to rural or outdoor settings. Further, travellers visiting endemic areas are at risk and diagnosis might be delayed or missed, because of non-suspect and lack of diagnostic serology, as there is no routine screening for TBE in non-endemic regions (92).

A report about retrospective testing of U.S. travellers to Europe and Asia between 2000-2009 revealed five cases of undetected TBE (93).

Once suspected, TBE can be diagnosed by detection of TBE-specific antibody constellation as reported above.

Diagnosis in vaccinated patients remains challenging due to a divergent behaviour of antibodies. An analysis of 39 patients with TBE vaccination break-through (VBT) infections showed: specific serum IgM antibodies were more often present in unvaccinated patients with TBE than in patients with VBT, while specific serum IgG antibodies were present in all TVB-patients, but only in 91% of unvaccinated patients (94). Levels of IgG antibodies were substantially higher in patients with VBT than in the unvaccinated patients. Further, antibody avidity was substantially higher in VBT-patients. Interestingly two VBT patients showed a completely different pattern of antibodies with both, specific serum IgM and IgG levels in the range seen in unvaccinated patients with TBE (95). This pattern has also been observed in other TBE VBT-studies and suggests that, in these cases, vaccination had not resulted in immunological priming (85).

1.3.6 Surveillance of TBE infections

ECDC provides an annual report about tick-borne encephalitis, that is published with a delay. The annual report for 2019 was published on 24th march 2021. Among 30 EU/EFTA countries 20 (67%) have surveillance systems for TBE developed of which 18 countries have a mandatory reporting system. In 2019, 3411 annual cases were recorded, 3246 of them were confirmed. Fatality rate was 0.7% and most cases were reported in Lithuania (25.4/100000 population) followed by Czech Republic (7.3/100000) and Estonia (6.2/100000). Immunisation status showed that 98.3% of cases were not vaccinated (96).

Several studies investigated the notable change in incidence rates and shift of endemic areas. In general, an increase of cases has been recorded during the last decades. It was

discussed that this might be caused by global warming, driving TBE gradually towards higher altitudes (97). Also, less extreme winters and longer spring and autumn seasons might promote TBE (98).

Other studies also suggested that TBE incidence rates might decrease in future decades. The fragile transmission cycles of TBEV may be disrupted since the expected rise in temperature and decrease in moisture appears to drive the distribution of TBEV into even higher-altitude regions and might therefore concern less people (99).

2 Results

This section is summarizing the results presented in the following published papers:
(*please also all original publications presented in section 4*)

Kohlmaier B., Schweintzger N.A., Zenz W. ***Measles recognition during measles outbreak at a paediatric university hospital, Austria, January to February 2017****. Eurosurveillance 25, 1900260 (2020), https://doi.org/10.2807/1560-7917.ES.2020.25.3.1900260*

Kohlmaier B., Svendova V., Walcher T. et al. ***A severe influenza season in Austria and its impact on the paediatric population: mortality and hospital admission rates, november 2017 - march 2018****. BMC Public Health 20, 178 (2020). https://doi.org/10.1186/s12889-020-8239-2*

Kohlmaier B., Schweintzger N.A., Sagmeister M.G. et al. ***Clinical Characteristics of Patients with Tick-Borne Encephalitis (TBE): A European Multicentre Study from 2010 to 2017.*** *Microorganisms 2021, 9, 1420. https://doi.org/10.3390/microorganisms9071420*

The study about measles recognition during the outbreak with thirteen confirmed measles patients in February 2017 showed that two had an atypical clinical picture. Of eight cases with no known epidemiological link, only one was diagnosed immediately; four were recognised with delay and three only retrospectively. Eleven typical measles cases had four

‘unrecognised visits’ to the outpatient clinic and 28 on the ward. Two atypical cases had two ‘unrecognised visits’ to the outpatient clinic and 19 on the ward. Thirteen clinicians did not recognise typical measles (atypical cases not included). Twelve of 23 physicians involved had never encountered a patient with measles before (27).

The study about influenza in the paediatric population during the season 2017/18 showed that Influenza-related paediatric hospitalisation rate in season 2017/18 was estimated as 128 (CI: 122–135) per 100,000 children, much higher than the national average of 40 per 100,000 over the years 2002–2016. There were nine reported influenza-associated deaths among children, resulting in a mortality rate of 0.67 (CI: 0.32–1.21) per 100,000 children (100).

The European multicentre study about clinical characteristics of patients with tick-borne encephalitis (TBE) showed that out of 555 patients with confirmed TBE 207 (37.3%) had meningitis, 273 (49.2%) meningoencephalitis, 15 (2.7%) meningomyelitis, and 58 (10.5%) meningoencephalomyelitis; In 2 patients with paresis no diagnosis could be established. 41 (7.4%) patients had a peripheral paresis of extremities, 13 (2.3%) a central paresis of extremities, and 25 (4.5%) had single or multiple cranial nerve palsies. Five (0.9%) patients died during acute illness. Outcome at discharge was recorded in 298 patients. Of 176 (59.1%) patients with incomplete recovery, 80 (27%) displayed persisting symptoms or signs without recovery expectation (76).

3 Discussion

3.1 Clinical characteristics

The presented studies include a detailed description of clinical characteristics of affected patients.

The measles study highlighted the importance of careful patient interviews and description of clinical signs and symptoms. The median incubation time of measles is 12.5 days, with a 95% CI from 11.8 days to 13.2 days. During the reported outbreak one patient had an incubation time of 23 days which was only one time reported before. (101,102). Out of 13 patients, 2 had an uncommon clinical presentation with atypical rash characteristics. One patient had an itching rash which was very uncommon. Literature research revealed only one publication that reported about itching rashes in measles patients (103). Another patient had an erythema exsudativum multiforme, which was described before but seems to be a rare clinical finding in measles patients (104,105). Several patients had co-infections including RSV infection, norovirus infection and urinary tract infections. Co-infections might be common in patients with measles infection but detailed descriptions or qualitative analysis are rare (106,107).

The study about paediatric influenza depicted a detailed description of clinical symptoms. We analysed reasons for hospital admission, among them high fever (32%), dyspnoea (19%), febrile seizure (12%), dehydration (10%) and diarrhoea or vomiting (9%) which confirmed observations from other countries (108). 15% of admitted children and about half of fatal cases had an underlying chronic disease. This confirmed international observation and contradicted the general populations belief, that influenza is harmless in previously healthy children and one of the least important childhood vaccinations (108–111).

The study about TBE in Europe included a detailed description of clinical signs and symptoms of patients with TBE. It was the first international multicentre study using a uniform case record form, which enabled us to describe the clinical characteristics with high quality. According to the reported findings, patients were allocated to different clinical diagnoses such as meningitis, meningoencephalitis, meningoencephalomyelitis. A

small proportion of patients (2.7%) had findings of myelitis without encephalitis, and was diagnosed as meningomyelitis. This entity has been described in various case reports but was very rarely reported before in cohort descriptions (112). We assume that in previous cohort descriptions, these patients have been included in the category 'meningoencephalomyelitis' and hope that our observation raises the awareness for a more accurate allocation to clinical diagnoses.

Further, the study revealed a high number of patients being discharged with incomplete recovery (59.1%), about half of them without expectation of recovery according to a clinician's assessment. Symptoms at discharge ranged from headache (93%) and decreased concentration (47%) to paresis of extremities (16%). This reflects a high burden of disease as reported before and stresses the meaning of primary prevention by vaccination (113).

3.2 Transmission and preventive measurements

The study about the measles outbreak confirmed the extreme high contagiousness of the measles virus which can survive in air in closed rooms up to 2 hours after a patient left as shown recently during the measles outbreak in 2019 (16,114). During the outbreak in 2017, most patients got infected in the waiting area of the outpatient clinic or hospital entrance area. Only one patient was infected by household transmission. Eleven of 13 patients were unvaccinated, including three infants not eligible for routine vaccination. This reflects a high protection rate in vaccinated patients and shows the necessity of re-vaccination after chemotherapy as seen in one health-care worker who got infected although she had been immunized as a child (115,116).

Because of the high transmission rates and high complications rates in infants, pregnant women and immunocompromised patients, a quick and careful exposure assessment is needed. All contacts must be investigated and assessed for eligibility of post exposure prophylaxis with measles active vaccination or passive immunisation with immunoglobulins. While active vaccination should be performed within 72 hours after exposure, immunoglobulins could be given up to 7 days after exposure or might be needed in immunocompromised patients and infants too young to be vaccinated (17).

Both prophylaxis, vaccination and immunoglobulins are highly effective and prevent most cases from transmission or mitigate an infection (114,117–119).
Further preventive measurements should include an isolation strategy in patients with fever and maculopapular rash and continuing training of health-care professionals to identify measles and conduct confirmation by laboratory testing.
Finally, vaccination remains the most effective preventive measurement in developed as well as in developing countries (14,37,120).

The study about paediatric influenza in the season 2017/18 revealed a high burden of influenza infections in children with high hospitalisation rates and 9 fatal cases. In course of this study a survey on the influenza vaccination status of patients at the Department of Paediatric and Adolescent Medicine Graz was conducted and showed that only 3 out of 100 children were vaccinated according to recommendations. This showed that vaccination rates are still considerably lower in Austria compared to other countries such as the USA with 57.8% of children 6 months to 17 years during the 2017–18 flu season (44). It must be assumed, that the low vaccination rate in Austria reflects the general population's attitude, that influenza in children is a harmless disease.

The study about TBE in Europe showed details on possible routes of transmission and confirmed tick-bites as the major route of transmission. All patients stayed in an endemic area and most patients (61%) reported a tick-bite, followed by a minority of patients (2%) with transmission by dairy products. Most likely, the rest of patients were also infected by tick-bites which happened unobserved. TBE-virus invades all tick tissues, also salivary glands, therefore, also a short-lasting tick-bite could lead to transmission of TBE-virus (121).
The best preventive measure of TBE is vaccination which is easily available and highly effective as also shown by our data with high rates of unvaccinated patients seen in our cohort (97.1%).

3.3 Diagnostic challenges

Although all investigated diseases are of viral origin, the diagnostic approach is quite diverse and each disease has its own challenges.

The study about the measles outbreak in 2017 revealed several pitfalls. Out of 13 patients, 7 had a delayed or missed diagnosis. The index patient, a 16-years old girl, reported an itching rash during her first presentation, which was interpreted as allergic reaction after a contact with bathing additives. As described above, itching has almost never been described before in measles patients. The second patient had also an untypical rash (erythema exsudativum multiforme). Further reasons for misdiagnosis or delayed diagnosis included co-infections (2 patients), suspected drug eruption (1 patient), bloody diarrhoea (1 patients) and an untypical long incubation time of 23 days (1 patient). Besides atypical presentation, clinicians were also challenged by the rare appearance of measles with 2 of 12 paediatricians in training and 9 out of 11 paediatric specialists who had never seen measles before. According to the results of our observation we concluded that a repeated awareness raising of measles for clinicians was needed and that thorough testing of all patients with symptoms suggestive for measles should be performed.

The study about paediatric influenza showed that patients presented with a wide range of symptoms but some main characteristics are seen in most cases including fever and signs of respiratory tract infection such as coughing and rhinitis (122). These symptoms are not disease specific but during an influenza season this combination represent a clear diagnostic hint and will prompt the treating clinician to test for influenza. Further, an epidemiological hint might help to raise the suspicion of influenza e.g. when an sibling or parent has already been diagnosed with influenza. According to current diagnostic practice testing for influenza is not obligatory, but since the introduction of easily accessible point-of care testing such as rapid tests and multiplex PCR, a routine testing for influenza has been integrated in many clinics during winter and spring season. As a positive side effect, this helps to monitor disease activity.

The study about TBE in Europe showed that reported symptoms are comparable to various other infections of the central nervous system. Borreliosis is an possible differential diagnosis and must be considered in patients with a history of tick-bite. Most patients with neuroborrelioses present with cranial nerve palsy, most commonly as facial palsy, but some patients also present with encephalitis, meningitis or myelitis (123). Therefore, testing of cerebrospinal fluid for borrelia specific IgM and IgG antibodies with matched serum samples is important to rule out borreliosis. Co-infections of TBE and neuroborreliosis have been reported which makes an assignment of clinical symptoms to each disease sometimes difficult (90). In our study, patients with co-infections with borrelia have been excluded, to provide a straight clinical description of TBE-patients.
Until today, Real-time-PCR testing is not part of clinical routine in TBE. It is described as an efficient method for detection in samples collected prior to the appearance of antibodies and might be used as an early diagnostics of TBE (124). Samples must be taken during a first viraemic phase, since it will yield negative results during neurological phase, when the virus has already been cleared from the blood and CSF (125). In clinical practice, PCR testing is not available and confirmation of TBE must be done by other laboratory tests such as detection of specific TBEV-antibodies by ELISA. This is reflected by our study, where none of the included 555 TBE patients was detected by PCR.

3.4 Disease surveillance

All three presented publications showed different important aspects of disease surveillance.

The study about measles recognition during a measles outbreak in 2017 showed important aspects of contact tracing. A detailed analysis of patient's records was necessary to reveal undiagnosed measles cases and demonstrate likely problems with the diagnosis of measles. Based on raised disease awareness, all measles cases were diagnosed during the following measles outbreak in 2019.

The study about paediatric influenza showed relevant advantages of active surveillance compared to passive surveillance. Our study was the first study using active surveillance methods in paediatric influenza in Austria. For this purpose, we contacted all Austrian paediatric hospitals. Although we did not achieve feedback from all hospitals the return rate was impressive and led to a better understanding of disease severity such as fatality rates and hospital admissions. In previous years number of influenza related deaths were analysed by ICD-10 coding, with an average of 1,33 paediatric deaths/year from 2002-2016, compared to 9 paediatric deaths in season 2017/18. As also reported by other Austrian institutes, we concluded that the 2017/18 season was a severe influenza season for children and adolescents, but a direct comparison of fatal cases with previous years remains difficult due to the different approaches of passive versus active surveillance. Hereafter, our observations and extensive description of paediatric influenza in Austria was the basis of governmental decision-making to provide the seasonal influenza vaccination free or charge to all children and adolescents.

The study about tick-borne encephalitis showed the high relevance of a uniform case definition and case record form (CRF). Using the common definition helped to achieve a comprehensive insight into the clinical course of tick-borne encephalitis in several endemic European countries.

3.5 Impact of publications

Vaccinations are one of the most effective methods in disease prevention and are considered as a major advance of modern medicine. All infectious diseases discussed in this thesis can be prevented by vaccination with high effectiveness or even eradicated, which has already been shown in the case of measles at least in some parts of the world. In order to expand disease prevention and increase vaccination rates, it is necessary to inform and update clinicians, health care authorities and the general public. All three publications covered different aspects aiming to raise the awareness for the disease and the possibility for vaccinations.

The detailed description of the measles outbreak in 2017 with identification of causes of non-recognition, lead to high attentiveness towards measles. Several lectures were held at the clinic and at conferences addressing specialists, as well as clinicians in training and students. In 2019, during the next measles outbreak at our clinic, all patients were recognized at first presentation and no further nosocomial transmission was recorded. Also, a talk was held at the Austrian Ministry of Health to emphasize the importance of the topic and promote future vaccination campaigns. Further, the outbreak investigation was published in a top ranked journal with open access to provide an international dissemination of our observations.

The outcome of our active surveillance of pediatric influenza cases during the season 2017/18 was presented at several congresses, at the Austrian Ministry of Health and to the general public. We showed the necessity for a vaccination campaign to raise public awareness and increase vaccination rate which was below 10% at that time. Further, the publication was open access to provide easy access to all interested persons and was cited by the Austrian Government as a basis of decision-making to provide Influenza vaccinations to all children and adolescents free of charge.

Tick-borne encephalitis (TBE) virus is one of the most common causes of viral meningitis and encephalitis in Europe. TBE vaccinations are highly effective, well tolerated and broadly available in endemic countries. The detailed clinical description of the course of disease provided high quality information about the potential severe course of disease with high rates of incomplete recovery at time of hospital discharge. Again, this work was published open access to provide easy access to all interested persons and can be used as basis for further vaccination campaigns.

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4 Attached publications

4.1 Measles recognition during measles outbreak at a paediatric university hospital, Austria, January to February 2017

4.2 A severe influenza season in Austria and its impact on the paediatric population: mortality and hospital admission rates, november 2017 - march 2018

4.3 Clinical Characteristics of Patients with Tick-Borne Encephalitis (TBE): A European Multicentre Study from 2010 to 2017

Measles recognition during measles outbreak at a paediatric university hospital, Austria, January to February 2017

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Recognition of measles is crucial to prevent transmissions in the hospital settings. Little is known about the level of recognition of measles and possible causes of not recognising the disease by physicians in the post-vaccine era. We report on a measles outbreak in a paediatric hospital in Austria in January to February 2017 with strikingly high numbers of not recognised cases. The extent and course of the outbreak were assessed via retrospective case finding. Thirteen confirmed measles cases were identified, two with atypical clinical picture. Of eight cases with no known epidemiological link, only one was diagnosed immediately; four were recognised with delay and three only retrospectively. Eleven typical measles cases had four 'unrecognised visits' to the outpatient clinic and 28 on the ward. Two atypical cases had two 'unrecognised visits' to the outpatient clinic and 19 on the ward.

Thirteen clinicians did not recognise typical measles (atypical cases not included). Twelve of 23 physicians involved had never encountered a patient with measles before. The direct and indirect costs related to the outbreak were calculated to be over EUR 80,000. Our findings suggest the need to establish regular training programmes about measles, including diagnostic pitfalls in paediatric hospitals.

Background

Despite elimination efforts, a considerable increase of measles cases in the European Union/European Economic Area (EU/EEA) countries was observed between January 2016 and March 2019 compared with previous years, with 44,074 measles cases being reported. Countries most affected were Romania, Italy, France, Greece, Germany and the United Kingdom [1]. Main risks for outbreaks include low vaccination coverage, importation of measles and nosocomial spread [2,3]. In a number of outbreaks, hospitals were amplifiers and healthcare workers (HCW) were infected [4,5]. Major reasons for measles transmission in hospitals are the high contagiousness of the measles virus, the capacity of the virus to persist in aerosol suspensions, unvaccinated healthcare personal, the nonspecific initial presentation of the patients, crowding of patients in outpatient clinics, inability to isolate febrile children from afebrile children in waiting rooms and the lack of awareness of physicians [2,6-9].

Typical measles symptoms include a prodromal stage with fever and upper respiratory symptoms, including coryza, conjunctivitis and a dry cough. After 2–4 days, a maculopapular rash starting from the face spreading down the body appears. The rash gradually recedes, fading first from the face and last from the thighs and feet. However, some patients might present with atypical symptoms, e.g. the rash might not start on the face or not be maculopapular (e.g. be purpuric instead). Patients with atypical measles symptoms or not presenting with full symptoms of the disease contribute to misdiagnoses during outbreaks [10,11].

Since 2015, Austria recommends the first dose of measles-mumps-rubella (MMR) vaccine at 9 months of age; however, MMR vaccination can be started at 6 months of age during a measles outbreak. First dose MMR vaccination coverage in children 2–5 years is 95%, but second dose coverage is only 84% [12].

Outbreak detection

In January 2017, we noticed a measles outbreak at the Department of Paediatrics and Adolescent Medicine with six cases occurring within 2 weeks, all without a known source of infection. Here we give a detailed outbreak description, including possible reasons for clinicians not recognising measles.

Methods

We performed a retrospective analysis of all patients visiting the Department of Paediatrics and Adolescent Medicine, Medical University of Graz from January to

March 2017 to describe the measles outbreak in early 2017.

We adhered to World Health Organization (WHO) definition by declaring a measles outbreak as two or more laboratory-confirmed cases that can be epidemiologically or virologically linked [13]. The outbreak time frame was defined from time of symptom onset of the first case until 21 days after the last case was diagnosed.

Case definition and genotyping

We used the European Centre for Disease Prevention and Control's (ECDC) measles case definition [14]. Measles infection was verified using real-time PCR (FTD Measles, Fast Track Diagnostics, Sliema, Malta) on throat swabs or ELISA (Enzygnost Anti-Measles Virus IgM and IgG, Siemens Healthcare Diagnostics, Marburg, Germany) on sera. Throat swabs were sent to the National Reference Centre for Measles, Department of Virology, the Medical University of Vienna for confirmation and strain analysis. Genotyping was performed according to the measles and rubella WHO reference laboratory recommendations [15] using the Measles Nucleotide Surveillance (MeaNs) database tool for sequence analysis of a 450 nt amplicon coding for the nucleoprotein (N-450).

The outbreak description included all patients with confirmed measles that were seen in our paediatric university hospital. Patients were numbered according to symptom onset.

Information on the number of reported measles cases in the district of Styria, Austria from 2009 to 2017 was provided by the Landessanitätsdirektion Graz, Austria.

Measles recognition

The analysis of measles recognition included all patients with confirmed measles and maculopapular rash, and excluded all patients with a known epidemiological link or referral with suspicion by a general practitioner or extramural paediatrician.

Diagnoses were categorised as 'immediately' if a measles patient was recognised at first presentation in exanthema stage or earlier, 'delayed' if a patient had at least one unrecognised visit in exanthema stage, and 'in retrospective' if a patient was diagnosed after acute measles during the retrospective outbreak investigation.

Retrospective data collection and analysis of medical records of measles cases was undertaken using the electronic documentation system openMEDOCS, containing information about all patients presenting at our hospital. Furthermore, we queried the database for measles notifications transmitted to the Austrian measles registration system from 27 January to 1 March 2017. Data collection and analysis were extended to 21 days after the last measles case was confirmed at our hospital in order to cover the maximum known incubation period [16]. Information on arrival and departure times of outpatient visits as well as admission times on the ward were collected in addition to immunisation status and demographic, epidemiologic and clinical information. Exposure was deemed to have occurred if a person was present with the source case, i.e. the primary case (P1), during an outpatient visit. We gathered information about the transmission routes by interviewing the patients' families.

For those patients who presented in exanthema stage and without a known epidemiological link or referral, the number of out- and inpatient visits where measles was not recognised together with the number of all involved clinicians was analysed.

We investigated the possible reasons for not recognising measles via a detailed review of all cases by two independent clinicians. The review procedure included a summary of all available medical documents and personal interviews with the treating clinician.

Measles experience of involved clinicians

We used an interview-delivered survey to collect data on the individual measles experience of clinicians involved in the management of the measles patients. In the interview, we asked about the total number of measles patients they had seen before and the length of time they had been practising medicine.

To investigate the economic impact of the not recognising measles of this outbreak, we analysed the direct and indirect costs related to it. The data collected included the costs of outpatient visits [17], costs of hospital stay on the general ward (as calculated by our hospital finance department), costs for antibody and PCR testing, costs associated with the estimated working hours for outbreak management and indirect costs from the productivity loss of parents, patients or both. The latter were calculated using a report about Austrian absences [18].

We investigated a measles outbreak in 2019 to compare our findings with this later outbreak. We analysed the visits of all cases in exanthema stage without a known epidemiological link or a referral. The 2019 outbreak was also from January to February and analysed in the same way as the 2017 outbreak. The total number of antibody and PCR tests was included in the analyses.

Statistical analysis

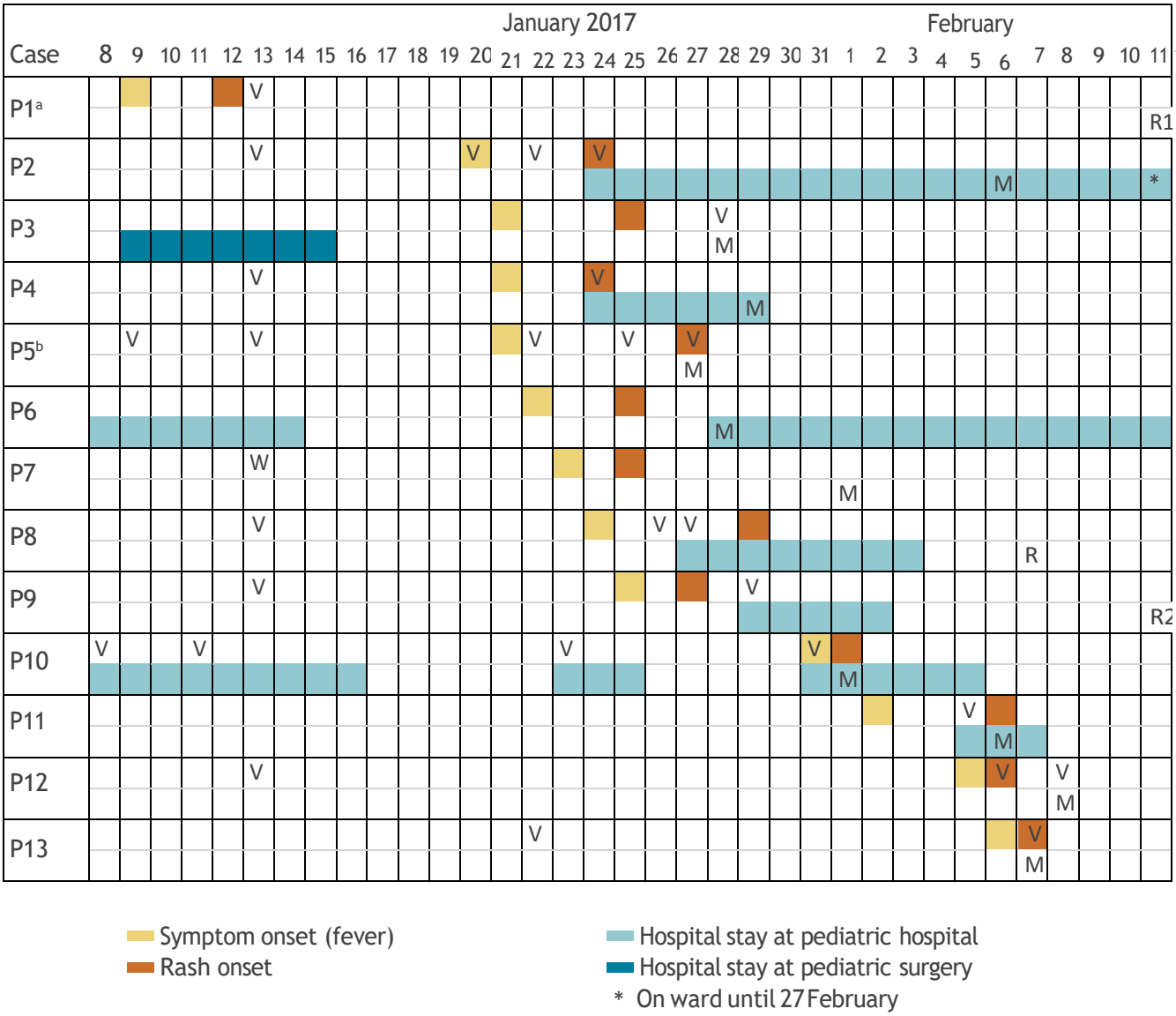
All data were anonymised and entered into a Microsoft Access database. Data were analysed using Excel and descriptive statistics.

Ethical statement

This study was approved by the local ethics committee of the Medical University of Graz (EK 30–062 ex 17/18). We have conducted this study consistent with the Declaration of Helsinki.

Figure 1

Timeline of symptoms onset, outpatient visits, hospital stays and measles testing of all measles patients, Styria, Austria, January to February 2017



M: testing for measles; R: retrospective testing for measles; R1: retrospective testing on 23 February; R2: retrospective testing on 30 March; V: visit in outpatient clinic; W: working in outpatient clinic.

[a] Source/primary case.

[b] Index case.

Results

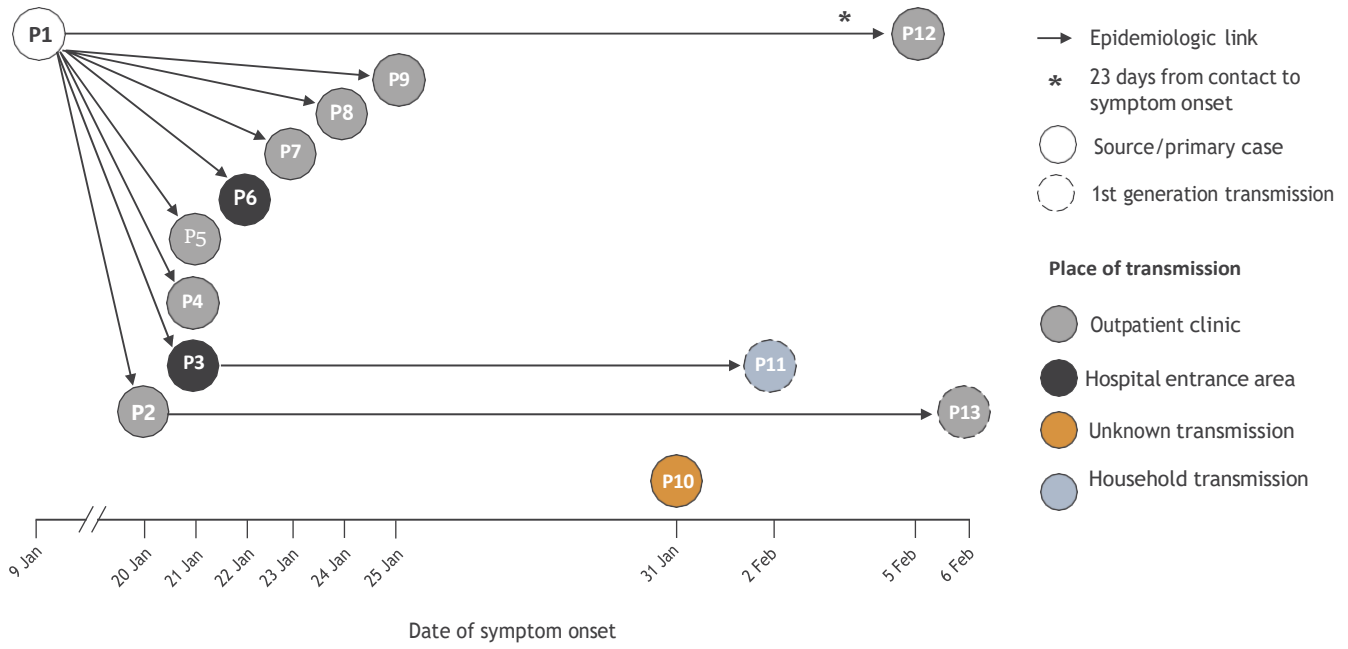
Thirteen measles cases presented to our Department of Paediatric and Adolescent Medicine between 13 January 2017 and 8 February 2017. All cases were laboratory confirmed. There were nine female and four male cases, with a median age of 12 months (range: 2 months–30 years). Six cases were infants under 1 year of age. Six cases became infected after visiting the outpatient clinic and two while hospitalised. One was a paediatrician in training. Eleven of 13 cases were unvaccinated, including three infants not eligible for routine vaccination. One case had received only one dose of MMR vaccine 9 years earlier. The paediatrician in training was fully vaccinated but received immunosuppressive treatment as a child.

Outbreak description

On 27 January 2017, the first measles case was diagnosed (index case, patient (P)5). Three days later, an additional three cases (P3, P4 and P6) were diagnosed. Five days after the first case, another two cases (P7 and P10) were diagnosed. None of the cases had a known source of infection.

Figure 2

Chain of measles transmission, Styria, Austria, January to February 2017 (n = 13)



P: patient.

The outbreak investigation was initiated after the first case was diagnosed, and discovered that three cases were treated in the outpatient clinic on 13 January 2017 for minor illnesses. By reviewing the medical records of all patients who were present on that day, we identified a teenager as the source case (P1). Measles was not recognised and P1 came into contact with 34 patients, infecting nine children.

Another six outbreak cases were identified (P2, P8, P9, P11, P12 and P13), two of which were diagnosed retrospectively (P8 and P9) (Figure 1 and 2).

Patient descriptions

P1 was a teenager who presented with fever, coughing and an itchy maculopapular rash that had appeared after taking a bath with an additive. P1 was diagnosed as febrile illness and allergic reaction to the bath additive. After being clinically identified as a possible source case, P1 tested positive for measles-specific IgM and IgG antibodies by ELISA. From interviews we learned that P1 was in the outpatient clinic for 4 hours and waited to be picked up for an additional 2 hours in the entrance area of the hospital. During the incubation period, P1 had met friends who recently had stayed in Romania, where a measles outbreak was reported [19].

P2 was a 12-month-old infant. Seven days after the presentation of the source case (APSC), P2 presented twice to the outpatient clinic with fever and also tested positive for influenza A virus through rapid antigen testing. Nine days APSC, P2 came to the outpatient clinic with persistent fever and oral mucositis, and 11 days APSC, the case presented at the outpatient clinic with fever, conjunctivitis, a maculopapular exanthema, diaper mucositis, hypoxaemia and oral aphthous ulcers. The case was hospitalised and diagnosed with influenza A infection and erythema exsudativum multiforme. Twenty-four days APSC, the treating physicians took a serum sample to measure herpes simplex virus (HSV) antibodies, describing a 'fever and rash' on the delivery note. The hygiene institute was aware of the measles outbreak and also tested for measles IgM. HSV-1 and measles IgM were both positive. This result was confirmed by a positive measles PCR in saliva. The case was classified as HSV-1 associated erythema exsudativum multiforme and measles infection. Through review of medical records, it was determined that P2 was in contact with the source case in the outpatient clinic.

P3 was a teenager, an inpatient at the paediatric surgery department and discharged from the hospital 2 days APSC. Thirteen days after release from hospital, the case was referred to the outpatient clinic by their practitioner with suspected measles because of fever and exanthema. Measles was verified by measles-specific IgM and IgG antibodies and PCR. The patient interview revealed that P3 was in contact with the source case at the entrance area.

P4 was a 9-month-old child. Eleven days APSC, P4 visited the outpatient clinic with fever, cough, full body rash and conjunctivitis. The case was diagnosed with

Table 1

Characteristics and diagnostic category of measles cases with possible reasons for delayed or not recognising measles, Styria, Austria, January to February 2017

Case	Age	Number of outpatient visits in prodromal stage	Number of outpatient visits in exanthema stage	Admission to hospital	Correct diagnosis	Laboratory confirmed	Diagnostic category[a]	Possible reason for delay or not recognising measles
P1	Teenager	0	1	No	Retrospective	IgM,IgG	Retrospective	Atypical measles
P2	Infant	3	1	Yes	On ward after 13 days	PCR, IgM, IgG	Delayed	Atypical measles
P3	Teenager	0	1	No	By referring paediatrician	PCR, IgM, IgG	Referred from paediatrician	NA
P4	Infant	0	1	Yes	On ward after 6 days	PCR, IgM, IgG	Delayed	Coinfection (UTI)
P5	Infant	2	2	No	At fourth outpatient visit	PCR	Delayed	Suspected drug eruption
P6	Early 30s	0	0	Yes	By referring GP	PCR, IgM, IgG	Referred from GP	NA
P7 (HCW)	Early 20s	NA	NA	NA	Themself	IgM, IgG	NA[b]	NA
P8	Infant	2	0	Yes	Retrospective	PCR	Retrospective	Coinfection (RSVandnorovirus)
P9	Infant	0	1	Yes	Retrospective	IgM	Retrospective	Bloody diarrhoea
P10	Infant	1	0	Yes	At first outpatient visit	PCR	Known epidemiological link	NA
P11	Teenager	1	0	Yes	At first outpatient visit	PCR	Known epidemiological link	NA
P12	Infant	0	2	No	At second outpatient visit	PCR	Delayed	Incubation period > 21 days
P13	10 years	0	1	No	At first outpatient visit	PCR	Immediately	NA

GP: general practitioner; HCW: healthcare worker; NA: not applicable; PCR: real-time PCR; RSV: respiratory syncytial virus; UTI: urinary tract infection; y: years.

[a] Excluding the specialist-in-training (P7).

[b] P7 was part of the outbreak but was not assigned a diagnostic category because this person, a clinician, self-diagnosed.

'fever without source' and admitted to the ward where a urinary tract infection with pyuria was detected. Sixteen days APSC, clinicians suspected measles. The diagnosis was verified by measles-specific IgM and IgG antibodies and PCR. Via review of medical records, it was determined that the case had contact with the source case in the outpatient clinic.

P5 was an 11-month-old infant who was seen four times in our outpatient clinic. Nine days APSC, the case presented with fever and obstructive bronchitis, 12 days APSC, P5 presented with mucositis and tonsillitis, and 14 days APSC, P5 presented with fever and a full body rash. The case was initially diagnosed with drug eruption because of cefaclor therapy. P5 returned to the clinic the same day and was diagnosed with measles, which was confirmed by PCR. Contact with the source case in the outpatient clinic was established.

P6 was a cystic fibrosis patient in their early 20s who was referred by their general practitioner with suspicion of measles on 28 January. P6 had fever and a maculopapular rash, and was hospitalised for 15 days. Measles was confirmed by PCR. The case was an inpatient when the source case presented to the hospital and met P5 in the entrance area.

P7 was a resident in their 30s. Ten days APSC, P7 had fever and went on sick leave. Twelve days APSC, P7 had a mild generalised maculopapular rash for 3 days. Nineteen days ASPC, the case suspected themself of having measles, which was confirmed by positive IgM antibodies. P7 had been vaccinated twice against measles but had undergone immunosuppressive therapy because of a malignancy during childhood. P7 met the source case when working in the outpatient clinic.

P8 was a 7-month-old infant. Thirteen days APSC, the case visited the outpatient clinic with fever, coughing and diarrhoea, and was diagnosed with a respiratory tract infection. The next day, P8 was admitted to the ward because of dehydration. The stool PCR was positive for norovirus and a throat swab PCR was positive for respiratory syncytial virus (RSV). Seventeen days APSC, the case was described as having a full body rash in the nursing report. Twenty-one days APSC, P8

Table 2

Measles cases reported by provincial public health authorities, Styria, Austria, 2009–2017

Year	Total number of cases	Number of cases 0–17 years of age
2009	32	27
2010	2	2
2011	18	9
2012	14	9
2013	8	4
2014	8	3
2015	31	22
2016	4	1
2017	33	15

was discharged with the diagnosis of RSV-positive bronchopneumonia. The rash, or any diagnosis referring to it, were not mentioned in the discharge letter. The outbreak investigation identified the patient as a possible measles case, which was confirmed by PCR from a preserved throat swab. The case was in contact with the source case in the outpatient department.

P9 was a 6-month-old infant. Sixteen days APSC, the case presented with subfebrile temperature over the previous 2 days, rhinitis, maculopapular rash, insufficient fluid intake and bloody diarrhoea. P9 was admitted to the ward and later discharged with a diagnosis of gastroenteritis. The rash was mentioned in the discharge letter but there was no diagnosis referring to the exanthema. Outbreak investigation identified P9 as a possible measles case, which was confirmed by retrospective blood testing for measles IgM. P9 encountered the source case in the outpatient clinic.

P10 was a 2-month-old infant. Eighteen days APSC, the infant's mother was diagnosed with measles in a different hospital (and is therefore not part of this analysis). The infant was admitted to our hospital for post-exposure prophylaxis with immune globulins. On the second day of P10's stay, the case developed a full-body rash and tested positive for measles by PCR. Outbreak investigation revealed that P10 was an inpatient with the mother the day when the source case presented. Upon interviewing, the mother reported that they had not left the ward that day. Our investigation could not identify the source of infection.

P11 was the teenage sibling of P3. Fifteen days after the onset of the sibling's symptoms, P11 presented in the outpatient clinic with fever. Measles was detected and confirmed by PCR and antibody testing 1 day after admission.

P12 was a 10-month-old infant. Twenty-three days APSC, the case developed a fever. The next day, the case presented in the outpatient clinic with a full-body rash and was diagnosed with viral exanthema. Two days later, P12 tested positive for measles by PCR. P12 met the source case in the outpatient clinic. The outbreak investigation could not determine any other contact to a measles case.

P13 was a 10-year-old child who presented 25 days APSC with fever and full body rash, and tested positive for measles by PCR. The child was in contact with P2 during their outpatient visit 9 days APSC.
All measles cases recovered uneventfully.

Genotype

Viral strain analysis supported the reproduced chain of transmission. All genotyped patients (P2, P3, P5 and P8) showed the same B3–4299 genotype. These sequences have been deposited in the WHO MeaNs database and assigned a MeaNs-ID: 103299, 103767, 103768 and 106868.

Recognition of measles patients in exanthema stage

Of 13 cases, one diagnosed themself (P7), two were referred with a suspicion of measles (P3 and P6) and two had a known epidemiological link (P10 and P11). Of the other eight, only one was diagnosed immediately (P13); four patients were diagnosed after delay (P2, P4, P5 and P12) and three were diagnosed retrospectively (P1, P8 and P9) (Table 1).

The analysis of 'unrecognised visits' of measles cases revealed six visits to the outpatient clinic and 47 on the ward. However, these visits includes two patients with atypical presentations (P1 and P2) who had two visits to the outpatient clinic and 19 visits on the ward. The 23 clinicians involved in the treatment of the measles cases were either paediatricians in training or paediatric specialists. In total, 18 clinicians did not diagnose measles, including eight paediatricians in training and 10 paediatric specialists. Excluding atypical cases (P1 and P2), 13 clinicians did not diagnose measles, including five paediatricians in training and eight paediatric specialists.

Possible reasons for the delayed diagnosis or not recognising measles

The retrospective outbreak investigation and interviews with all involved clinicians revealed a high number of not diagnosed patients. For P1 and P2, atypical clinical presentations were identified as the most likely reason for not recognising the disease. A specialist did not diagnose measles in P1 because of the uncharacteristic itchy rash and the bathing with eucalyptus additive.

P2 had erythema exsudativum multiforme and no typical rash. Pictures taken from the rash were reviewed and classified as atypical. According to literature research, erythema exsudativum multiforme or Steven Johnson Syndrome can appear in measles patients, but their appearance seems to be rare [20,21].

Table 3

Costs of the measles outbreak, Styria, Austria, January to February 2017 (n = 13 cases)

Service	Costs (EUR)/unit	Amount	Total (EUR)
Outpatient visits	142.08/visit	21 visits	2,983.68
Inpatient stays	808.43/stay	82 stays	66,291.26
Serological testing	8.34/test	16 tests	133.44
PCR testing	40.19/test	46 tests	1,848.74
Outbreak management	66.27/hour	80 hours	5,301.60
Productivity losses of parents or patients	127.50/day	62 days	7,905.00
Total	NA	NA	84,463.72

NA: not applicable.

In P4 and P8, co-infections were identified as a possible reason for not recognising measles. P4 had a urinary tract infection, and P8 was positive for RSV and norovirus which would explain coryza and gastrointestinal symptoms.

The measles rash of P5 was interpreted as drug eruption from cefaclor, while P9 was diagnosed as having gastrointestinal infection because of bloody diarrhoea. Measles was not suspected in P12 because of the incubation period, which was beyond 21 days.

Clinician experience with measles

All 23 clinicians, 11 paediatric specialists and 12 paediatricians in training, who were involved in the management of the measles patients were asked whether they had seen a measles case before. Nine of 11 paediatric specialists, but only 2 of 12 paediatricians in training had seen measles before. The median working years of paediatric specialists was 15 years (range: 6–31) while the median number of working years of paediatricians in training was 2 years (range: 1–5). The median number of measles patients seen by paediatric specialists was two (range: 1–30). One paediatrician in training had seen one patient and the other had seen five.

Number of measles cases in Styria from 2009–2017

According to the records of the province of Styria public health authorities, there have been a total of 150 measles cases from 2009 to 2017, with a median annual incidence rate of 1.4 cases per 100,000 population (Table 2).

Economic impact of the measles outbreak

The evaluation of costs directly and indirectly related to the outbreak revealed a total amount of EUR 84,463.72 (Table 3). Inpatient stays and loss of productivity totalled EUR 74,196.26. Twenty-one outpatient visits cost a total of EUR 2,983.68 while measles testing cost EUR 1,982.18, only accounting for 2% of the total costs. Forty-six patients were tested by PCR and 16 for measles IgM antibodies via ELISA.

Comparison with the 2019 measles outbreak

In January 2019, a measles outbreak with 18 cases was seen at our hospital. Seven cases presented without a known measles contact and without referral from a GP or external paediatrician. All cases were recognised at first presentation. Five clinicians were involved in the diagnosis of cases, including four paediatric specialists and one paediatrician in training. All but one paediatric specialist were also involved in the outbreak in 2017. During the outbreak in 2019, we tested 129 patients by PCR and 33 for measles IgM antibodies.

Outbreak control measures

After the 2017 outbreak, there was an intensified training course about measles with three sessions that aimed to reach many hospital employees. Three educational sessions were held. The first, held as part of our weekly education sessions, was about measles in general with a focus on providing clinical information, e.g. measles symptoms, incubation period and presentation of cases. A second session was held during our weekly presentation of interesting clinical cases, which is also a lecture for students. The third session was held as part of our yearly meeting for new diagnostic and treatment algorithms. All sessions were held within 1 year of the outbreak, and all included general measles information and detailed clinical descriptions of all cases seen at our department. We also monitored the attendance of clinicians. Of 114, 71 (62%) clinicians employed in our hospital participated in at least one session.

Discussion

This article reports on the recognition of measles cases in a paediatric department at a central European university hospital in the ‘post-vaccination era’. It shows that only one of eight cases without a known epidemiological link or without referral from GP or external paediatrician was diagnosed immediately. We retrospectively identified and diagnosed the source case during the outbreak investigation and were able to establish a transmission chain. The isolated strain was prevalent in the latest Romanian measles outbreak that began in 2016, with 19,443 reported cases, 11,217

confirmed cases and 63 deaths from January 2016 to October 2019 [22]. Strain analysis of measles cases in neighbouring provinces of Austria showed different genotypes (personal communication, Heidemarie Holzmann, November 2017), substantiating our established transmission chain [23].

Incubation periods ranged from 7 to 23 days in P12, which, while unusual, but has been reported [24].

One healthcare worker who was fully vaccinated became infected. Although they were working while in the prodromal stage for 1 day, no onward transmission was observed. Previous reports suggest low transmission rates in breakthrough infections [25]. No other hospital employee became infected which might be the consequence of a rigorous vaccination status control of hospital employees that was established after a measles outbreak in 2015. Positive vaccination status verified by record of two doses of MMR or a protective measles titre, is a mandatory requirement for new applicants at our hospital. Mandatory vaccination in health providers is a key measure to reduce the risk of nosocomial transmissions from healthcare workers [26].

Besides a lack of experience and awareness, we identified further possible causes for not recognising measles: atypical presentations, co-infections and suspected allergic reaction to medications. Two patients had atypical presentations although they were not vaccinated and were not immunosuppressed. Literature quantifying the number of patients with atypical presentations is scarce and the prevalence of such might be subject to vaccination rates. P1 presented with an itchy rash which is uncommon. A literature review revealed only one article describing an itching character of the measles exanthema [27].
P2 presented with erythema exsudativum multiforme. After positive testing for measles IgM measles were discussed, but because of the clinical picture of erythema exsudativum mulitfomre the test was considered to be false positive. However, the additional positive measles PCR substantiated the positive serology. This patient was seen by four paediatricians in training and six paediatric specialists, including a paediatric infectious disease specialist on 20 visits before diagnosing measles.

Co-infections are common in measles infections [28,29] which can mislead a clinician's assessment of the symptoms. One case presented with a urinary tract infection and another one with bronchopneumonia caused by RSV and norovirus gastroenteritis; one measles case diagnosed with tonsillitis was treated with cefaclor and the maculopapular rash was interpreted as antibiotic-induced exanthema. A correct differential diagnosis cannot be based solely on a clinical investigation, and in cases of doubt, measles should always be considered [30,31].

Clinicians should test for measles in patients with atypical symptoms, especially during outbreaks to avoid further spread and unnecessary inpatient stays of undiagnosed cases. Moreover, our findings support a thorough testing of patients with symptoms suggestive for measles since costs for testing were relatively small compared with costs related of not recognising measles and/or diagnostic delay.

Not recognising measles cases might be because of a prolonged period free from measles. The disease has become rare in Austria, as suggested by the number of measles cases in the province of Styria (Table 2). A tendency towards a more accurate diagnosis over time was observed. The last outbreak case, P13, was the only case diagnosed without delay and P12's diagnostic delay was shorter compared with the average diagnostic delay.

The education sessions held after the outbreak were effective and a reminder that measles should be considered in patients with fever and maculopapular rash. During the measles outbreak in 2019, there were no cases with delayed diagnosis in our hospital. The analysis of PCR and antibody testing showed a higher rate of testing, reflecting increased disease awareness.

There are several limitations to this study. The improved recognition of measles may be a combination of pre-existing clinician diagnostic skills as well as an increased awareness for measles during the course of the outbreak. Analysis of recognition of only sporadic cases would provide more accurate evidence for increased awareness. Moreover, consecutive visits of a patient are difficult to interpret as independent events, as previous visits are apparent to the treating clinicians. The cost analysis is subject to estimation and did not consider workload associated with additional vaccinations, consultations or other healthcare providers.

Conclusion

This outbreak shows a need for repeated awareness-raising of measles for clinicians in paediatric hospitals to ensure adequate diagnosis and awareness for the need to isolate patients with exanthema ahead of establishing a diagnosis. Training programmes should include pictures of rashes to identify measles patients, an emphasis on the necessity for proper history taking, as well as considerations of the possible pitfalls of patients with atypical presentations. Finally, our findings suggest thorough testing of all patients with symptoms suggestive for measles. The costs for testing were relatively small compared with costs related to not recognised cases and/or diagnostic delay.

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Conflict of interest

None declared.

Authors' contributions

BK investigated the outbreak, analysed the data and wrote the manuscript. NS co-wrote the manuscript, contributed to multiple drafts and corrected the manuscript. WZ designed the study, analysed the data, and contributed to multiple drafts.

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A severe influenza season in Austria and its impact on the paediatric population: mortality and hospital admission rates, november 2017 - march 2018

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Abstract

Background: In Austria paediatric influenza-associated hospitalisations and deaths have never been systematically monitored. We examined the influenza season 2017/18 in terms of hospitalisation and mortality in the Austrian paediatric population and put the results into perspective of the available data from the last 15 years.

Methods: Cases of influenza-associated hospitalisations and deaths for season 2017/18 in children below 18 years were retrospectively collected from 12 and 33 Austrian hospitals, respectively. Hospitalisation and mortality rates for the whole Austrian paediatric population were estimated, adjusting for the population in each catchment area. Two Austrian databases were queried for hospitalisations and deaths associated with influenza during 2002–2016. Rough estimate of the vaccination coverage was calculated from a survey on 100 inpatients.

Results: Influenza-related paediatric hospitalisation rate in season 2017/18 was estimated as 128 (CI: 122– 135) per 100,000 children, much higher than the national average of 40 per 100,000 over the years 2002– 2016. There were nine reported influenza-associated deaths among children, resulting in mortality rate of 0.67 (CI: 0.32–1.21) per 100,000 children.

What is known:

- Children are among the most affected by the seasonal influenza outbreaks worldwide.
- Vaccination coverage against influenza in Austrian children is very poor (last reported below 5%).
- There is no active surveillance of influenza associated hospitalisations and mortality in Austria.

What is new:

- This work is the first active monitoring of paediatric influenza associated hospitalisations and mortality in Austria.
- An analysis of data from two Austrian databases showed a median number of paediatric influenza- associated deaths of 1 (ranging from 0 to 4 cases) over the years 2002–2016.
- An especially severe influenza season 2017/18 resulted in more than 2000 hospitalisations and nine paediatric deaths.

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Background

Seasonal influenza is an infectious disease caused by influenza viruses, causing a high rate of deaths and hospital admissions worldwide [1]. Children are among the most affected during the annual outbreaks: a recent meta-analysis estimated that one in ten of all unvaccinated children is infected by seasonal influenza every year [2].

Hospitalisation and mortality in paediatric patients with influenza represent only a small proportion all influenza cases [3] Both are widely influenced by patient specific factors like age and comorbidities [4, 5].

Large amount of literature on hospitalisation and mortality rates focuses on the United States [6–12]. Latest study reported annual mortality of 0.15 per 100,000 children [13]. In Europe, several country-based studies reported influenza-related paediatric hospitalisation or mortality rates [14–17], but these data are lacking in many other European countries, including Austria.

In Austria, mortality rates due to influenza during 2001–2009 were estimated to be 15.5 deaths per 100,000 people of all ages [18]. Despite several Austrian agencies monitoring cases of influenza-like illness, such as Austrian Agency for Health and Food Safety (AGES) or Diagnostic Influenza Network Austria (DINÖ), there are no published data on paediatric hospitalisation and mortality due to influenza.

Since 2013 influenza vaccination is recommended for all children from 6 month of age in Austria [19]. However, general vaccination recommendation is not linked to governmental funding for vaccination and influenza vaccination is not covered by the general health insur- ance. Information about influenza vaccination rates are derived from numbers of sold vaccines and implicate a very low vaccination rate [20].

In our study, we aimed to systematically monitor influenza-associated pediatric deaths and estimate influenza-associated pediatric hospitalisations to raise the awareness of the burden of paediatric influenza. We estimated influenza-related hospitalisation rates based on retrospectively collected data from Austrian paediatric hospitals which participated in our survey and compared the findings to the data from the years 2002–2016. We described prospectively collected inpatients from the Department of Paediatric and Adolescent Medicine, Medical University of Graz, in greater detail, including crucial clinical parameters. We reported on influenza-associated fatalities among children during 2017/18, collected prospectively, and compared to the historical data from 2002 to 2016, collected retrospectively. Our secondary aim was to obtain a rough estimate of vaccination coverage, by conducting a survey among the general inpatients in the paediatric hospital in Graz.

Methods

To assess hospitalisation and mortality rates in Austria, we prospectively recorded the data from our local hospital in Graz, and sent a survey asking for influenza related hospitalisations and deaths to all 50 paediatric hospitals listed by the Austrian Society of Paediatrics and Adolescent Medicine. Data from the hospitals that replied to our survey were then extrapolated to the whole Austrian population. Patient's age range was set to 0–17 years according to the Austrian law, which states that patients younger than 18 years should be admitted to paediatric hospitals, whereas older patients should be admitted to adult hospitals.

Clinical description of inpatients with influenza at the Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Austria, 2017/18

All paediatric inpatients at the Department of Paediatric and Adolescent Medicine, Medical University of Graz aged less than 18 years with virologically confirmed influenza infection were prospectively recorded during the influenza season from the 1st of November 2017 till the 31st of March 2018. All patients were reviewed by a physician and classified according to ECDC (European Centre for Disease Prevention and Control) case definition [21] and their clinical data were documented. Influenza infection was confirmed either by rapid antigen test with nasopharyngeal swabs (sensitivity 66.1% and specificity 98.3% for children [22], or by PCR from blood. The choice of test was based on clinician's judgement. Since the vaccination status of inpatients had been recorded incompletely during their hospital stay, a telephone survey was conducted after discharge asking the parents about the influenza vaccination history of their children.

Estimation of influenza-associated hospitalisations in Austria, 2017/18

We aimed to obtain hospitalisation rates from all 50 Austrian paediatric hospitals, nevertheless, we did not get response from all of them and had to estimate the nation-wide hospitalization rates. We used the information system of the Austrian Health Research Institute, Gesundheit Österreich Forschungs- und Planungs GmbH (GOEG), to find out the number of paediatric inhabitants in the catchment area of each hospital. We estimated the total number of paediatric inpatients with influenza infection in 2017/18 using Poisson regression with the population of each catchment area as an offset variable, and reported the 95% confidence interval (CI). We had to resort to using the population data from 2017 as seasonal population data were not available. We calculated the hospitalisation rate per 100,000 children as $100{,}000 * (h/N)$, where h was the estimated number of

hospitalized influenza patients and N the Austrian population under 18 years of age.

Influenza-associated paediatric mortality in Austria, 2017/18

To investigate the total number of paediatric influenza-associated deaths in Austria for the season 2017/18, an email survey was conducted among all 50 paediatric hospitals in Austria. The survey included age, sex, relevant chronic conditions, influenza subtype, vaccination status and cause of death. In centres with lethal cases, a treating physician was asked to review the cases. As we did not get a response from all the hospitals, we again estimated the total number of lethal cases using Poisson regression with the population of each catchment area as an offset variable, and reported the 95% confidence interval (CI). We calculated the mortality rates per 100,000 children as $100,000 * (d/N)$, where d was the estimated number of lethal cases and N the Austrian population below 18 years of age (in 2017).

Influenza-associated paediatric hospitalisation and mortality rates in Austria, 2002–2016

For comparison with previous seasons, we used data from GOEG once again to find the number of paediatric influenza-associated inpatients and number of deaths for each year from 2002 to 2016. GOEG queried two databases - Statistics Austria and the Federal Ministry of Labour, Social Affairs, Health and Consumer Protection (BMASGK) - using the following search criteria: cause of death with ICD-10 coding J09, J10 and J11 as main or secondary diagnosis. In case of discrepancy in death counts between the two databases, the higher number was taken.

Estimation of paediatric vaccination coverage in Austria 2017/18

The latest published estimates of paediatric vaccination coverage in Austria, 3.43 and 4.30%, were described for the season 2010/11 [17, 18]. Austria did not provide the data to ECDC for the latest seasons, hence we have no information about the current vaccination coverage. In order to obtain at least a rough estimate of more recent vaccination rates, clinicians in our hospital randomly asked parents of 100 paediatric inpatients older than 12 months and younger than 18 years (hospitalized for any reason except for influenza), whether their children were vaccinated against influenza, and, for comparison, tick-borne encephalitis (TBE) and measles, mumps and rubella (MMR). The confidence interval of a child being vaccinated was constructed using exact binomial test.

Results

Clinical description of paediatric inpatients with influenza at the Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Austria, 2017/18

From November 1st 2017 to March 31st 2018 a total of 708 paediatric patients with virologically confirmed influenza infection were seen at the Department of Paediatric and Adolescent Medicine, Medical University of Graz. These patients had a total of 800 outpatient visits (1.13 visits per patient). 166 (23% of all patients) were admitted to the ward (for inpatient characteristics and age distribution see Table 1 and Fig. 1, respectively). One hundred forty-five patients (89%) were positively diagnosed via rapid antigen test, 17 (10%) via PCR and 4 patients (1%) via both of these tests. We were able to reach parents of 125 inpatients (75%) for a query about vaccination against influenza. Only one of these 125 patients had been vaccinated against influenza in the season 2017/18. Reasons for hospital admission included high fever (32%), dyspnea (19%), febrile seizure (12%), dehydration (10%) and diarrhea or vomiting (9%). Rare reasons included sepsis, suspected meningitis, myocarditis, myositis, hematemesis, reaction to oseltamivir, and reduced general condition. 23 (15%) inpatients had an underlying chronic condition including 8 patients with

Table 1 Characteristics of 166 inpatients with virologically confirmed influenza infection of the Department of Paediatric and Adolescent Medicine, Medical University of Graz, Austria, from November 2017 to March 2018

Number of patients	166
Age: median (IQR)	2 years (1–5)
Gender (male)	94 (57%)
Subtype - A	112 (68%)
Subtype - B	49 (30%)
Subtype - A + B	2 (1%)
not known	3 (2%)
Hospital stay: median (IQR)	2 days (2–4)
Paediatric intensive care unit (PICU)	9 (5%)
Hospital stay on PICU: median (IQR)	6 days (3–8)
Antibiotics on PICU	8 (89% of PICU patients)
Invasive ventilation	2 (1%)
Non-invasive ventilation	2 (1%)
Oxygen therapy	10 (6%)
Max. CRP (mg/l): median (IQR)	8.2 (2.95–21.20)
Leukocytes (G/l): median (IQR)	7.3 (5.4–10.6)
Antibiotics before admission	16 (10%)
Antibiotics on ward	38 (24%)
Deaths	1 (1%)
Vaccinated	1 out of 166

CRP C-reactive protein, *IQR* interquartile range

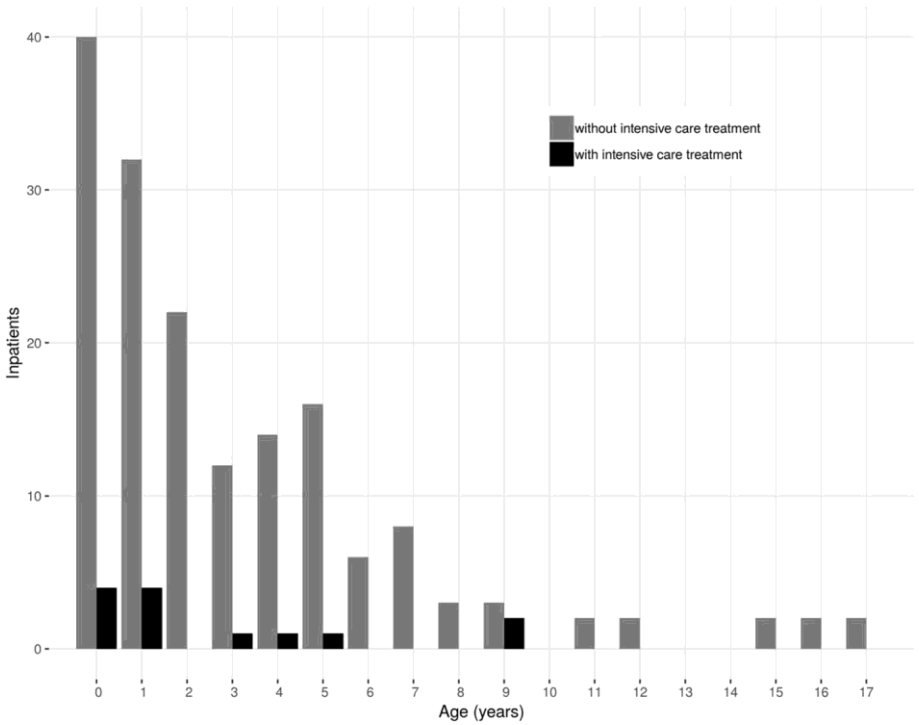

Fig. 1 Age distribution of influenza-related paediatric hospitalisations in Graz, Austria

developmental delay. Nine children (5.4% of all inpatients) needed intensive care treatment including one child who died from acute necrotizing encephalitis and three patients who had chronic conditions, in particular chronic kidney disease, De-Morsier-Syndrome and spastic quadriplegia. Two patients needed invasive ventilation for a total of nine and ten days, and two patients needed non-invasive ventilation (Optiflow™ | Fisher & Paykel Healthcare).

Estimation of influenza-associated paediatric hospitalisations in Austria, 2017/18

We contacted 50 Austrian paediatric hospitals in order to obtain the numbers of influenza inpatients for the 2017/18 season. However only 12 (24%) hospitals responded to our survey and reported their counts (see Table 2). Due to the geographical distribution of the hospitals, located in north, middle and south parts of Austria, we consider these hospitals to be a representative subsample of all paediatric hospitals in Austria. We estimated the absolute number of influenza inpatients in Austria for the 2017/18 season to be 2072 (CI: 1968–2179). Hospitalisation rate was then 128 (CI: 122–135)

per 100,000 children.

Influenza-associated paediatric deaths in Austria, 2017/18

All 50 paediatric hospitals were contacted and 33 replied. There were nine reported lethal cases, five males and four females, median age of 4 years. Three children had no underlying disease, one had a congenital autoinflammatory syndrome and five neurodevelopmental delay. Cause of death was in four cases acute respiratory distress syndrome, in two cases elevated intracranial pressure, in two cases asphyxia and in one case pneumonia. Subtype A was the most prevalent type of influenza

Table 2 Reported numbers of influenza-associated inpatients from 12 Austrian paediatric hospitals and population below 18 years of age in their catchment area from November 2017 to March 2018

Hospital	Influenza inpatients	Population
Graz LKH	166	147,715
Wien SMZ OST Donauspital	129	78,046
Linz BSRV KH	81	52,895
St. Pölten UnivKL	64	41,010
Leoben-Bruck/Mur LKH	62	50,557
Steyr LKH	56	21,221
Wien SMZ SÜD KFJ/Preyer	46	45,724
Wels-Grieskirchen KL	38	47,206
Ried/Innkr BSRV KH	32	23,103
Tulln UnivKL	31	31,708
Kirchdorf/Krems LKH	25	10,942
Oberwart LKH	12	29,707
Total	*742*	*579,834*

virus (7 patients–78%), one patient had subtype B and one had both subtypes positive. See Table 3 for all relevant characteristics of the cases. Vaccination status was available from six children and none of them was vaccinated against influenza. We estimated the absolute number of influenza-related deaths inpatients in Austria for the 2017/18 season to be 11 (CI: 5–20). Mortality rate was then estimated as at least 0.67 (CI: 0.32–1.21) per 100,000 children.

Influenza-associated paediatric hospitalisation and mortality rates in Austria, 2002–2018

Database search results from GOEG showed a median of 675 (ranging from 224 to 1653 cases) influenza paediat- ric inpatients and median of 1 (ranging from 0 to 4 cases) influenza-associated deaths over the years 2002– 2016. Hospitalisation and mortality rates were calculated per 100,000 children (Table 4) and depicted on Figs. 2 and 3. The comparison of both databases we queried for number of deaths (Statistics Austria and BMASGK) are shown in Table 5.

Estimation of vaccination coverage in Austria 2017/18

The survey among inpatients in the paediatric hospital in Graz showed that only three out of 100 patients were correctly vaccinated against influenza, while 85 against TBE and 90 against MMR. The probability of a child be- ing vaccinated against influenza was estimated as 0.03 with 95% confidence interval (0.016–0.113).

Discussion

In this study, we describe the influenza season 2017/18 in Austria, resulting in nine reported paediatric influenza-associated deaths and approximately 2072 hospitalisations of children. We showed that the calculated paediatric hospitalisation and mortality rates (128 and 0.67 per 100,000 children, respectively) were several times above the national average, calculated over the last 15 years.

It is important to acknowledge the differences in data collection for years 2002–2016 (retrospective) and season 2017/18 (prospective), hence possible underestimation of the counts in the 2002–2016 time range. The conclusions of our results are, nevertheless, supported by the reports of exceptionally severe influenza season 2017/18 in Austria [23] as well as in Germany [24], the whole of Europe [25] and the United States [26].

The observed number of paediatric influenza-associated deaths during the season 2017/18 exceeded the number of the Austrian paediatric deaths in the year 2017 caused by the following vaccine preventable diseases combined: measles, rubella, hepatitis A, hepatitis B, poliomyelitis, pertussis, diphtheria, and infections with *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* [unpublished data from GOEG].

A recent study estimated that vaccination against influenza could reduce the paediatric mortality by 50% or by 65% in children with or without an underlying disease, respectively [11]. Despite Austria's recommendations to vaccinate all people older than 6 months against influenza, the country has been described as resistant against influenza prevention and control [27]. Also, there is little information about influenza vaccination rates in the Austrian population. The European Centre for Disease Prevention and Control (ECDC) published a report on influenza vaccination rates during seasons 2007–2008, 2014–2015 [28] and 2015–16,
2016–17 [25]. Austria was among the few European countries recommending influenza vaccination for all children older than 6 months [19], yet in both ECDC reports failed to provide an estimation of vaccination coverage for the study. The latest published estimates of paediatric vaccination coverage in Austria were approximately 4% for season 2010/11 (3.43 and 4.3% [29, 30]), the lowest coverage among all age groups. There is no other more recent published source of vaccination rates in Austrian children.

Table 3 Characteristic of influenza-associated paediatric deaths in Austria in the influenza season from November 2017 to March 2018

Age (years)	Sex	Subtype	Relevant chronic conditions	Vaccinations against influenza	Cause of death
3	m	A + B	trisomy 21	not vaccinated	cerebral abscess
3	f	A	none	not vaccinated	acute stenosing laryngotracheitis
3	m	A	developmental delay	not vaccinated	ARDS
4	m	A	autoinflammatory syndrome	not vaccinated	pneumonia
4	f	A	tetraspastic paresis	not known	ARDS
4	f	A	none	not vaccinated	cerebral pressure
5	m	A	Bardet-Biedl syndrome	not known	ARDS
10	f	A	tetraspastic paresis	not vaccinated	ARDS sepsis
12	m	B	asthma	not known	severe asthma

ARDS acute respiratory distress syndrome, *f* female, *m* male

Table 4 Influenza-associated paediatric inpatients and deaths in Austria between 2002 and 2018. The number of inpatients and deaths in Austria during season 2017/2018 was estimated from reported cases in 12 and 33 Austrian hospitals, respectively, while the cases in 2002–2016 were collected retrospectively by searching ICD-10 codes

Year	Number of Inpatients	Number of inpatients per 100,000 children	Number of deaths	Number of deaths per 100,000 children
2002	582	35.7	0	0.00
2003	912	56.2	1	0.06
2004	880	54.4	2	0.12
2005	747	46.3	2	0.12
2006	344	21.4	1	0.06
2007	548	34.4	0	0.00
2008	487	30.9	1	0.06
2009	1653	105.8	4	0.26
2010	224	14.5	0	0.00
2011	764	50.1	3	0.20
2012	665	44.1	1	0.70
2013	681	45.4	2	0.13
2014	349	23.4	0	0.00
2015	676	45.3	2	0.13
2016	867	57.3	1	0.70
11/2017 03/2018	2072 (CI: 1968-2179)	128 (CI: 122–135)	11 (CI: 5–20)	0.67 (CI: 0.32–1.21)

Our survey on the influenza vaccination status at the Department of Paediatric and Adolescent Medicine Graz showed only 3 out of 100 children as being vaccinated according to vaccination recommendations. This suggests that the vaccination coverage has not increased since the latest report from 2011 [30].

In comparison, the same survey showed that 85 out of 100 children were correctly vaccinated against tick-borne encephalitis and 90 against measles, mumps, and rubella (MMR). This implies that the Austrian public is highly susceptible to governmental vaccination recommendations for preventable diseases.

The failure to increase the vaccination coverage for influenza in Austrian adults has been ascribed to ignorance of the health care system, a lack of social marketing and, as a consequence, an underestimation of the seriousness of the disease by the general public [31].

Limitations

Our study has several limitations. Only 24 and 66% of paediatric hospitals responded to our survey on hospitalisation and mortality, respectively, hence we had to estimate the total number of inpatients and deaths, reporting the 95% confidence interval as a variability measure.

Another limitation is that the frequency of testing for influenza viruses might differ between hospitals, resulting in a reduced detection rate of influenza cases. Also, when comparing season 2017/18 to the previous years, it is important to point out that the data collection for the

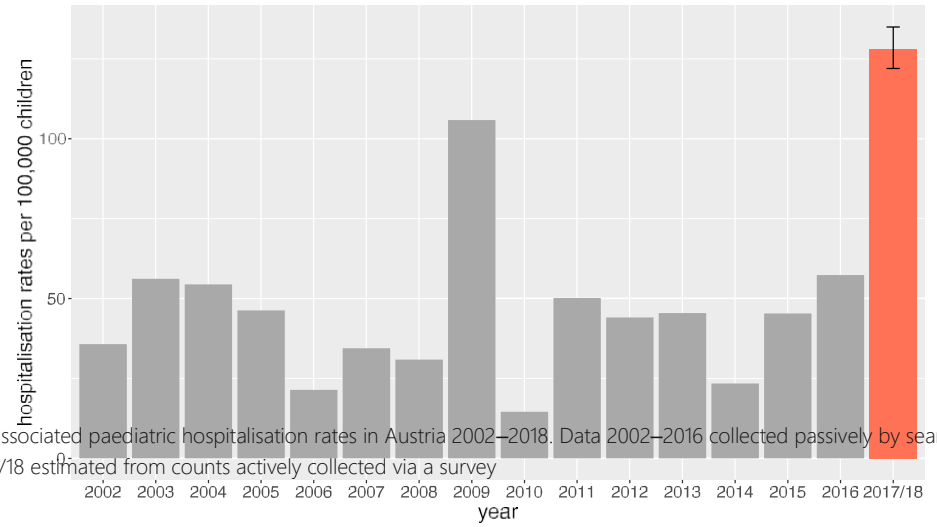

Fig. 2 Influenza-associated paediatric hospitalisation rates in Austria 2002–2018. Data 2002–2016 collected passively by searching ICD-10 codes, data 2017/18 estimated from counts actively collected via a survey

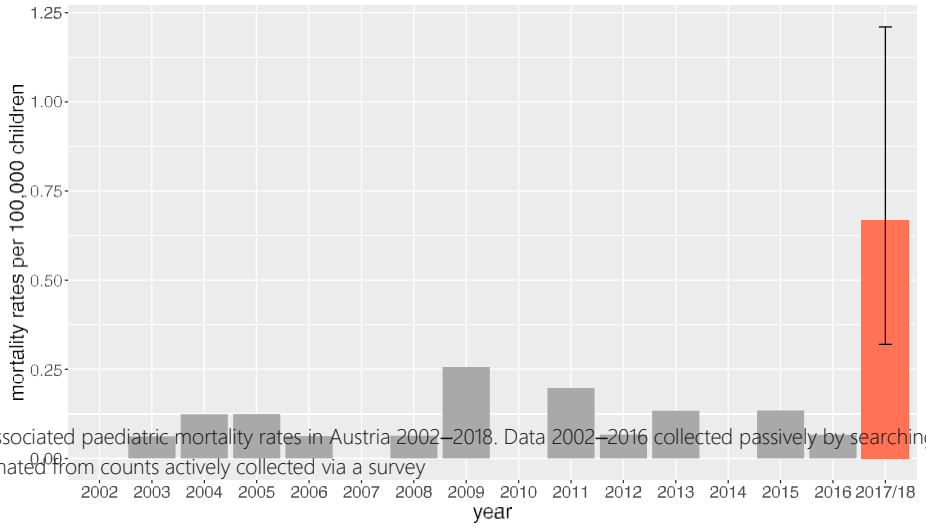

Fig. 3 Influenza-associated paediatric mortality rates in Austria 2002–2018. Data 2002–2016 collected passively by searching ICD-10 codes, data 2017/18 estimated from counts actively collected via a survey

years 2002–2016 was performed passively by searching for ICD-10 codes, whereas the data for season 2017/18 were collected actively via a survey. Therefore, a direct comparison of differences between 2002 and 2016 and season 2017/18 might be exaggerated. It remains unclear if the lower number of inpatients and lower death rate in previous seasons were due to underreporting or due to a milder course of disease. Despite this limitation, we show the comparison for argument's sake.

Table 5 Influenza-associated paediatric deaths in Austria between 2002 and 2016 – comparison of two databases

Year	Number of deaths according to BMASKG[a]	Number of deaths according to Statistics Austria
2002	0	0
2003	1	1
2004	2	0
2005	2	0
2006	1	0
2007	0	0
2008	1	0
2009	4	3
2010	0	0
2011	3	3
2012	1	0
2013	1	2
2014	0	0
2015	1	2
2016	1	1

[a] Federal Ministry of Labour. Social Affairs, Health and Consumer Protection

The conducted survey about the vaccination rate of inpatients is limited by the small number of participants, the preselected participants including only patients treated at our hospital and the exclusion of infants. Despite the limitations of the survey, we included its results to have a rough estimate of vaccination rates, since there is no publication available about actual influenza vaccin- ation rates in children in Austria.

Here we describe patients with influenza not regarding other co-infections including other respiratory diseases. Co-infections are common and in some cases the severity of diseases and need for inpatient treatment could be influenced by the combination of pathogens.

Conclusion

In summary, our data from the severe influenza season of 2017/18 emphasize the burden of paediatric influenza in Austria. We suggest a paediatric influenza surveillance network to be established, providing continuous reports and easy access to the public, similar to the one in the United States [32]. Such surveillance should include diagnosed paediatric cases, paediatric hospital admis- sions, patients requiring intensive care, and paediatric influenza-associated deaths.

Abbreviations

AGES: Austrian Agency for Health and Food Safety; BMASGK: Federal Ministry of Labour, Social Affairs, Health and Consumer Protection; DINÖ: Diagnostic Influenza Network Austria; ECDC: European Centre for Disease Prevention and Control; GOEG: Gesundheit Österreich Forschungs- und Planungs GmbH; ICD: International Statistical Classification of Diseases and Related Health Problems; IQR: Interquartile range; MMR: Measles, mumps and rubella;
PCR: Polymerase chain reaction; TBE: Tick-borne encephalitis

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Authors' contributions
provided data (HP, LK, HK, KZ, WZ + influenza network), collected data (BK, TW, WZ), analysed data (VS, BK, TW), wrote the manuscript (BK, VS, WZ), supervised the analysis (WZ). All authors have read and approved the final manuscript.

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Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available due to individual patient protection but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was approved by the local Ethical Committee of the Medical University of Graz (EC-Nr. 30–263 ex 17/18).

Consent for publication
Patient's data is retrospectively reported in anonymous form. No informed consent was necessary.

Competing interests

WZ received financial support for organizing the „Graz vaccination day "from GSK, Pfizer, Merck, and Sanofi. The remaining authors have no conflicts of interests.

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Clinical Characteristics of Patients with Tick-Borne Encephalitis (TBE): A European Multicentre Study from 2010 to 2017

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Abstract: Tick-borne encephalitis (TBE) virus is a major cause of central nervous system infections in endemic countries. Here, we present clinical and laboratory characteristics of a large international cohort of patients with confirmed TBE using a uniform clinical protocol. Patients were recruited in eight centers from six European countries between 2010 and 2017. A detailed description of clinical signs and symptoms was recorded. The obtained information enabled a reliable classification in 553 of 555 patients: 207 (37.3%) had meningitis, 273 (49.2%) meningoencephalitis, 15 (2.7%) meningomyelitis, and 58 (10.5%) meningoencephalomyelitis; 41 (7.4%) patients had a peripheral paresis of extremities, 13 (2.3%) a central paresis of extremities, and 25 (4.5%) had single or multiple cranial nerve palsies.

Five (0.9%) patients died during acute illness. Outcome at discharge was recorded in 298 patients. Of 176 (59.1%) patients with incomplete recovery, 80 (27%) displayed persisting symptoms or signs without recovery expectation. This study provides further evidence that TBE is a severe disease with a large proportion of patients with incomplete recovery. We suggest monitoring TBE in endemic European countries using a uniform protocol to record the full clinical spectrum of the disease.

Keywords: tick-borne encephalitis; vaccine-preventable disease; meningomyelitis; central paresis; peripheral paresis

1. Introduction

Tick-borne encephalitis (TBE) is an infection of the central nervous system (CNS) caused by the tick-borne encephalitis virus (TBEV) being transmitted by ticks in several central, eastern, and northern European countries [1,2]. The severity of the disease is broad, ranging from fever and headache to death, with a relatively high proportion of patients needing intensive care unit (ICU) treatment. Most patients develop meningitis or meningoencephalitis, some present with additional spinal involvement. At hospital discharge, many patients suffer persisting signs like ataxia and tremor; symptoms such as headache or decreased concentration are also described [3–5]. In addition, follow-up studies have shown that 16–50% of patients suffer from long-lasting sequelae [6–11]. Since the 1970s, a highly effective vaccine against TBE has been available and has led to a significant decrease in cases in countries with high vaccination rates [12]. Nevertheless, TBE remains an important issue caused by climate change and residual low vaccination rates in several endemic countries [13,14]. Therefore, continuous monitoring and detailed clinical analysis are needed to inform health care professionals and public authorities. To the best of our knowledge, hitherto, only national or single-center studies describing clinical details of TBE have been published. Here, we present a detailed description of clinical characteristics of a large international cohort of patients fulfilling the European Centre for Disease Prevention and Control (ECDC) case definition for confirmed TBE by using a common clinical protocol.

2. Materials and Methods

2.1. Establishment of a Uniform Case Record Form (CRF) and Patient Recruitment

In 2013, the international network "European genetics study of tick-borne encephalitis" (EU-TICK-BO) was established to investigate host genetic associations with the susceptibility and severity of TBE. To provide a consistent description of TBE patients across all centers, a uniform patient case record form (CRF) was established (Supplementary CRF). Paper CRFs were filled out by the treating clinicians and entered into an electronic database. In participating centers (Table S1), patients were prospectively collected between January 2014 and December 2017. A retrospective cohort was collected, starting from January 2010. We used the ECDC case definition for TBE [1]. Clinical criteria included any person with symptoms or signs of inflammation of the CNS (e.g., meningitis, meningoencephalitis, meningoencephalomyelitis). Laboratory criteria included at least one of the following: specific IgM and IgG antibodies in blood; specific IgM antibodies in cerebrospinal fluid (CSF); seroconversion or four-fold increase of TBE-specific IgG antibodies in paired serum samples. We included only patients with confirmed TBE, meeting the clinical and laboratory criteria. Patients with a history of TBE vaccination were enrolled if infection with TBEV was demonstrated either by an increase of TBEV IgG antibodies in convalescent serum, by demonstration of TBEV-IgM in CSF, or by proof of a positive TBE-specific IgG antibody CSF/serum index [15].

2.2. Quality Control

Data integrity and plausibility were reviewed by two clinicians from the lead study center. A list of missing items and unclear issues was sent out to each participating center. If the centers were not able to provide a complete basic dataset (age, gender, admission date, reliable laboratory evidence of a recent TBEV infection, and symptoms/signs in acute stage), their patients were excluded.

2.3. Patient Assessment

The findings of each patient in the neurological phase were reviewed, and the following diagnoses were assigned (modified according to Günther et al. 1997) [16]: meningitis, moderate meningoencephalitis, severe meningoencephalitis, meningomyelitis, meningoencephalomyelitis with moderate encephalitis, and meningoencephalomyelitis with severe encephalitis. The following signs indicated moderate encephalitis: Glasgow Coma Score (GCS) ≥ 9, ataxia, tremor, dysphagia, or single cranial nerve palsy. Severe encephalitis was characterized by GCS < 9, seizures, central paresis, mechanical ventilation, multiple cranial nerve palsies, or bulbar symptoms.

Pareses of extremities were categorized as peripheral paresis (a patient with flaccid paresis of an extremity/extremities without signs of corresponding lesions in brain imaging, if available) or central paresis (a patient with a spastic paresis of extremities, with signs of corresponding lesions in brain imaging, if available). At discharge from hospital, patients were categorized into "complete recovery" if symptoms or signs of TBE completely vanished or "incomplete recovery at discharge" when TBE symptoms or signs were still present. Patients with "incomplete recovery at discharge" were further categorized into "complete recovery expected" and "incomplete recovery expected" based on the assessment of the treating physician. Persisting symptoms or signs at discharge were categorized into "mild subjective" if patients had one or two subjective symptoms, "severe subjective" with three or more subjective symptoms, and "objective" if at least one objective sign with or without subjective symptoms was observed. The main foci of this work were "findings in acute disease", "outcome at discharge", and "blood and CSF findings". Only "findings in acute disease" were recorded in all included patients.

2.4. Statistical Analysis

Differences in patient characteristics in acute disease and outcome at discharge were analyzed with the Kruskal–Wallis test with Dunn's multiple comparisons test for continuous variables and Fisher's exact or Pearson's chi-squared test for categorical variables. The Kruskal–Wallis test, with Dunn's multiple comparisons test, was performed to examine the differences in blood and CSF levels according to diagnostic groups. For binary data, p-values (p), together with odds ratios (OR) and their confidence intervals (CI), were reported. Statistical analyses were conducted in R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism software version 8 (GraphPad Software, La Jolla, CA, USA).

2.5. Literature Review

To set our findings in context with previously published TBE cohort descriptions, a literature search was conducted on PubMed using the search term "(tick borne encephalitis [Title/Abstract])". Titles were screened for cohort descriptions using original patient data. Information about frequency of diagnosis (meningitis, meningoencephalitis, meningoencephalomyelitis, meningomyelitis), paresis, and fatality rates were extracted from full articles from selected abstracts. We included original articles published between 1975 and 2020, with cohort sizes of at least 20 TBE patients presumably infected by the European subtype of TBEV.

2.6. Ethical Statement

The study was approved by the local ethics committee of each center, and appropriate informed consent was obtained from all participating patients.

3. Results

3.1. Patient Characteristics and Findings in Acute Disease

A total of 1045 patients with TBE were recruited for genetic investigations (EU-TICK-BO); 430 of a single center were excluded as they only participated in the genetic analysis; 17 patients were excluded due to their date of admission before 2010 and 43 because of an incomplete basic data set after quality control. Finally, 555 (420 prospectively and 135 retrospectively recruited) cases were eligible for clinical description (Table 1), with ages ranging from 11 months to 88 years (median of 50 years, interquartile range (IQR) 36–61). Overall, 23 patients were younger than 15 years; 144 (25.9%) patients had comorbidities or conditions: 95 (17.1%) had a cardiovascular disease, 17 (3.1%) had a pre-existing neurological disease, 11 (1.9%) had a respiratory disease, 10 (1.8%) had a hematological disease, and 8 (1.4%) had other comorbidities (5 patients with renal disease, 2 patients with immunodeficiency and 1 patient with immunosuppression treatment after organ transplant). Three (0.5%) patients were pregnant.

Table 1. Details of TBE patients, including basic characteristics, course of disease, severity of acute disease, paresis and spinal involvement, and outcome at discharge.

Basic Characteristics	**All Patients (*n* = 555)**
gender, female (%)	223 (40)
age, years (range)	50 (0–88)
BMI in adults, median (IQR)	26 (23–29) *
comorbidity (%)	144 (26)
TBE vaccination–any (%)	16 (2.9) *
tick bite noticed (%)	273 (61) *
transmission by dairy products (%)	11 (2)
course of disease	
biphasic course (%)	329 (65) *
hospital stay (days), median (IQR)	10 (8–13) *
ICU admission (%)	38 (7) *
ICU length of stay median, days (IQR)	5 (2–8) *
diagnosis	
meningitis (%)	207 (37.3)
meningoencephalitis, moderate (%)	241 (43.4)
meningoencephalitis, severe (%)	32 (5.8)
meningomyelitis (%)	15 (2.7)
meningoencephalomyelitis, moderate encephalitis (%)	46 (8.3)
meningoencephalomyelitis, severe encephalitis (%)	13 (2.3)
unknown (%)	2 (0.2)
neurological deficiencies	
peripheral paresis (%)	41 (7.4)
central paresis (%)	13 (2.3)
unknown peripheral or central paresis (%)	2 (0.2)
single cranial palsy (%)	19 (3.4)

Table 1. *Cont.*

Basic Characteristics	All Patients (*n* = 555)
multiple cranial palsies (%)	6 (1.1)
disturbance of sensibility (%)	20 (5) *
bladder dysfunction (%)	20 (5) *
pain in extremities (%)	17 (4) *
respiratory paresis (%)	9 (2) *
rectal dysfunction (%)	9 (2) *
outcome at hospital discharge	
complete recovery (%)	117 (39) *
incomplete recovery (%)	176 (59) *
death (%)	5 (2)

* Number of available observations: all patients: *n* = 555, except BMI (*n* = 315), TBE vaccination status (*n* = 546), tick bite noticed (*n* = 444), course of illness (*n* = 504), length of hospital stay (*n* = 316), ICU admission (*n* = 554), length of ICU stay (*n* = 34), respiratory paresis (*n* = 419), bladder dysfunction (*n* = 420), rectal dysfunction (*n* = 419), disturbance of sensibility (*n* = 418), pain in extremities (*n* = 414), and outcome at hospital discharge (*n* = 298).

Sixteen (2.9%) patients had TBE despite being vaccinated. Out of these, seven were vaccinated as recommended, six had no complete basic vaccination, and three had their last booster vaccination not according to the recommendation. Most patients had a biphasic course of disease (65.1%), with various symptoms or signs, including fever, fatigue, malaise, headache, body pain, pharyngitis, and gastrointestinal symptoms (Table 1).

A clinical diagnosis was assigned to 553 of 555 patients; 207 (37.3%) had meningitis (M), 241 (43.4%) moderate meningoencephalitis (ME mod.), 32 (5.8%) severe meningoencephalitis (ME sev.), 15 (2.7%) meningomyelitis (MM), 46 (8.3%) meningoencephalomyelitis (MEM) with moderate encephalitis, and 13 (2.3%) meningoencephalomyelitis with severe encephalitis. In two patients, a differentiation of peripheral from central paresis was not possible, and these patients were classified as "unknown". The distribution of diagnoses according to age is shown in Figure 1.

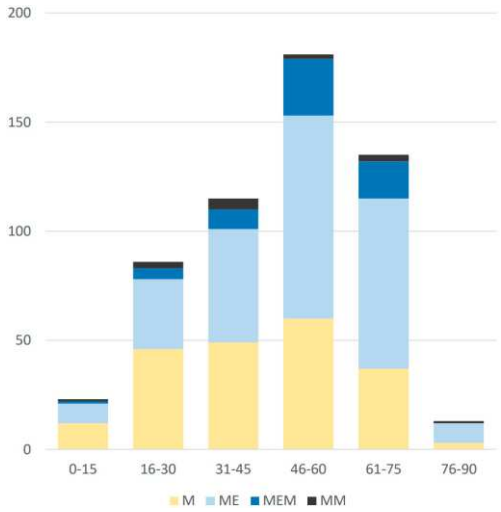

Figure 1. Distribution of clinical diagnosis according to age groups.

3.2. Patients with Pareses at Acute Phase of Disease

In total, 56 (10.1%) patients had pareses of extremities, of whom 41 (7.4%) had peripheral pareses of extremities, 13 (2.3%) central pareses of extremities, and 2 had unknown peripheral or central pareses of extremities (Table 2). A detailed distribution of pareses

of extremities is shown in Table 2. Twenty-five (4.5%) patients had cranial nerve palsy. Nineteen of them had a single cranial nerve palsy, and six had multiple cranial nerve palsies. Further details about cranial nerve palsies were not recorded.

Table 2. Findings in patients with TBE in the initial phase and in the neurological phase.

Initial Phase	***n* (%)**
no initial phase	175 (35)
fever	275 (55)
fatigue	221 (44)
malaise	188 (37)
headache	211 (42)
body pain	134 (27)
pharyngitis	70 (14)
gastrointestinal symptoms	58 (12)
Neurological Phase	
fever	501 (94)
headache	509 (95)
nausea or vomiting	323 (61)
nuchal rigidity	396 (74)
positive Kernig sign	208 (40)
disturbance of consciousness	134 (24)
ataxia	206 (37)
tremor	210 (38)
single cranial nerve palsy	20 (4)
dysphagia	9 (2)
severe CNS dysfunction (GCS < 9)	13 (2)
seizures	8 (1)
central paresis	10 (2)
respiratory failure (in need of mechanical ventilation)	7 (1)
multiple cranial nerve palsies	6 (1)
bulbar palsy	15 (3)

CNS = central nervous system; GCS = Glasgow Coma Score. Number of available observations: in initial phase: initial phase recorded (n = 505), including fever (n = 328), fatigue (n = 326), malaise (n = 327), headache (n = 329), body pain (n = 327), pharyngitis (n = 326), gastrointestinal symptoms (327); findings in neurological phase: fever (n = 535), headache (n = 534), nausea or vomiting (n = 530), nucheal rigidity (n = 532), positive Kernig's sign (n = 521), disturbance of consciousness, ataxia, tremor, single cranial nerve palsy and dysphagia (n = 553), severe CNS dysfunction (n = 552), seizure (n = 554), central paresis (n = 553), respiratory failure (n = 553), multiple cranial nerve palsies (n = 552), and bulbar palsy (n = 552).

3.3. Spinal Involvement

Spinal involvement was observed, including paresis of extremities (as reported), disturbance of sensibility (n = 20), bladder dysfunction (n = 20), pain in extremities (n = 17), respiratory paresis (n = 9), and rectal dysfunction (n = 9).

3.4. Correlation of Clinical Diagnosis

The following characteristics and findings were significantly associated with clinical diagnosis: patients with M were younger than patients with ME ($p < 0.0001$), and patients with MEM ($p = 0.002$) had lower rates of comorbidities (OR = 0.52, $p = 0.004$ and OR = 0.46, $p = 0.03$, respectively) and were less often admitted to the intensive care unit

(ICU) (OR = 0.07, $p < 0.0001$ and OR = 0.10, $p = 0.006$, respectively) (Table 3). At discharge, patients with M had higher rates of complete recovery than patients with ME (OR = 2.64, $p = 0.0006$) and patients with MEM (OR = 13, $p < 0.0001$). Further, patients with ME had higher rates of recovery compared to patients with MEM (OR = 2.6, $p = 0.0006$) (Table 3). Accordingly, patients with M had lower rates of incomplete recovery than patients with ME (OR = 0.38, $p = 0.0006$) and patients with MEM (OR = 0.07, $p < 0.0001$) (Table 3). Further patient characteristics, including gender, body mass index (BMI), and vaccination status, were not associated with specific clinical diagnoses.

Table 3. Comparison of patient characteristics, course of disease, and result at discharge from hospital according to clinical diagnosis.

	Meningitis (*n* = 207)	**Meningoencephalitis (*n* = 273)**	**Meningomyelitis (*n* = 15)**	**Meningoencephalo-myelitis (*n* = 58)**	**Significance**
patient characteristics					
gender female (%)	77 (37)	124 (45)	4 (27)	18 (31)	$p = 0.074$
age median (IQR)	44 (29–57)	53 (41–63)	45 (30–64)	54 (44–63)	**$p < 0.0001$** *
BMI in adults, median (IQR)	25 (23–29)	26 (23–28)	24 (22–27)	26 (24–30)	$p = 0.52$
comorbidity (%)	38 (18)	82 (30)	5 (33)	19 (33)	**$p = 0.011$** *
TBE vaccination, any (yes/no)	4 / 203	9/260	1 / 13	2 / 55	$p = 0.40$
tick bite noticed (yes/no)	98 / 55	138/95	9 / 1	29 / 20	$p = 0.21$
transmission by dairy products (%)	6 (3)	4 (1)	0	1 (2)	n.a.
course of disease					
biphasic course (yes/no)	116 / 69	168 / 81	9 / 5	36 / 20	$p = 0.77$
hospital stay median (IQR)	9 (8–11), $n = 85$	10 (8–13), $n = 187$	12 (10–18), $n = 6$	11 (9–17), $n = 38$	**$p = 0.013$** *
ICU admission (%)	2 (1)	30 (11)	1 (7)	5 (9)	**$p < 0.0001$** *
ICU length of stay median, days (IQR)	3	5 (2–7)	n.a.	4 (2–12)	$p = 0.35$
outcome at discharge from hospital					
complete recovery (%)	50 (60)	60 (36)	3 (43)	4 (10)	**$p < 0.0001$** *
incomplete recovery (%)	33 (40)	104 (62)	4 (57)	35 (88)	**$p < 0.0001$** *
death (%)	0	4 (2)	0	1 (3)	$p = 0.28$

Abbreviations: n.a., not applicable. * Details on significance: age median: M vs. ME ($p < 0.0001$) and M vs. MEM ($p = 0.002$); comorbidity: M vs ME (OR = 0.52, CI = 0.32–0.82; $p = 0.004$); M vs. MEM (OR = 0.46, CI = 0.23–0.94; $p = 0.03$,); hospital stay: M vs. MEM ($p = 0.023$); ICU admission: M vs. ME (OR = 0.07, CI = 0.009–0.31; $p < 0.0001$) and M vs. MEM (OR = 0.10, CI = 0.01–0.7; $p = 0.006$); complete recovery at hospital discharge: M vs. ME (OR = 2.64, CI = 1.5–4.7; $p = 0.0006$); M vs. MEM (OR = 13, CI = 4.1–55; $p < 0.0001$); ME vs. MEM (OR = 2.6, CI = 1.5–4.7; $p = 0.0006$); incomplete recovery at hospital discharge: M vs. ME (OR = 0.38, CI = 0.21–0.68; $p = 0.0006$,); M vs. MEM (OR = 0.07, CI = 0.02–0.24; $p < 0.0001$).

3.5. Outcome at Discharge

We recorded the outcome at the discharge of 298 patients; 117 (39%) had a complete recovery, 176 (59%) an incomplete recovery, and 5 (2%) died. Based on the treating physician's assessment, 96 (32%) patients were discharged with "complete recovery expected", while 80 (27%) were discharged with "no recovery expected" (Table 4).

Table 4. Comparison of patients with complete recovery, incomplete recovery, and death.

Basic Characteristics	Complete Recovery (*n* = 117)	Incomplete Recovery (*n* = 176)	Death (*n* = 5)	Significance
female (%)	48 (41)	80 (45)	2 (40)	$p = 0.74$
median age in years (IQR)	50 (28–64)	51 (40–61)	48 (43–73)	$p = 0.46$
comorbidity (%)	36 (31)	54 (31)	4 (80)	$p = 0.076$
TBE vaccination (%)	8 (7)	7 (4)	0	$p = 0.45$
tick bite noticed (%)	77 (66)	103 (59)	3 (60)	$p = 0.42$
diary product (%)	2 (2)	5 (3)	0	$p = 0.73$
course of Disease				
biphasic course	81 (70)	114 (65)	3 (60)	$p = 0.63$
median BMI (IQR)	26 (23–29)	26 (24–29)	28 (22–35)	$p = 0.95$
median hospital stay in days (IQR)	10 (8–12)	10 (8–14)	10 (9–11)	$p = 0.12$
ICU admission (%)	8 (7)	20 (11)	4 (80)	**$p = 0.0003$ ***
median days on ICU (IQR)	5 (3–5)	4 (2–7)	10 (9–11)	$p = 0.18$
diagnosis				
meningitis (%)	50 (42)	33 (19)	0	**$p < 0.0001$ ***
meningoencephalitis (%)	60 (51)	104 (59)	4 (80)	$p = 0.26$
meningomyelitis (%)	3 (3)	4 (2)	0	$p > 0.99$
meningoencephalomyelitis (%)	4 (4)	35 (20)	1 (20)	**$p < 0.0001$ ***
pareses				
central paresis (%)	0	9 (5)	1 (20)	**$p = 0.0036$ ***
peripheral paresis (%)	1 (2)	25 (14)	1 (20)	**$p < 0.0001$ ***
cranial nerve palsy (%)	2 (2)	15 (9)	0	**$p = 0.049$ ***
spinal involvement				
respiratory paresis (%)	1 (1)	7 (4)	0	$p = 0.26$
bladder dysfunction (%)	4 (3)	13 (7)	0	$p = 0.40$
rectal dysfunction (%)	1 (1)	6 (3)	0	$p = 0.33$
disturbance of sensibility	1 (1)	6 (3)	1 (20)	$p = 0.06$
pain in extremities	1 (1)	16 (9)	0	**$p = 0.006$ ***

* Details about significance: ICU admission: death vs complete rec. (OR = 49.9, CI = 4.3–2651; $p = 0.0002$); death vs incompl. rec. (OR = 30, CI = 2.8–1530; $p = 0.001$); diagnosis meningitis: incomplete rec. vs complete rec. (OR = 0.3, CI = 0.17–0.54; $p < 0.0001$); diagnosis meningoencephalomyelitis: incomplete rec. vs complete rec (OR= 7, CI = 2.4–28; $p < 0.0001$); central paresis: incomplete rec. vs complete rec (OR = infinity, CI = 1.4-infinity; $p = 0.012$); death vs. complete rec. (OR = infinity, CI= 0.6-infinity, $p = 0.041$); peripheral paresis: incomplete rec. vs complete rec. (OR= 19, CI = 3–792; $p < 0.0001$); cranial nerve palsy: incomplete rec. vs complete rec. (OR = 5.3, CI = 1.2–49; $p = 0.02$); pain in extremities: incomplete rec. vs complete rec. (OR = 12, CI = 1.7–490, $p = 0.002$).

Symptoms and signs of 121 patients discharged with incomplete recovery were recorded (Table 5); 36 (30%) had mild subjective symptoms, 28 (23%) had severe subjective symptoms, and 57 (47%) had objective signs, of whom 25 (20.5%) had one objective sign, 25 (20.5%) had two objective signs, and 7 (6%) had three or more objective signs. Headache (93% of patients) was a predominant subjective symptom, followed by decreased concentration (47%). Objective signs included tremor (31%), ataxia (22%), and pareses of extremities (16%) (Table 5).

Table 5. Symptoms and signs of TBE in patients discharged with incomplete recovery.

	Patients (*n* = 121)
Subjective Symptoms	***n* (%)**
headache	112 (93)
decreased concentration	57 (47)
decreased stress tolerance	27 (22)
increased irritability	21 (17)
decreased memory	32 (26)
emotional instability	24 (20)
sleep disturbance	39 (32)
objective Signs	
dysarthria	2 (2)
dysphagia	0
diplopia	2 (2)
hemiparesis	2 (2)
cranial nerve palsy—ocular	0
cranial nerve palsy—facial	3 (2)
cranial nerve palsy—pharyngeal	0
ataxia	27 (22)
tremor	38 (31)
hemihypaesthesia	2 (2)
paresis of extremities	19 (16)
disturbance of sensibility	4 (3)
bladder dysfunction	1 (1)
bowel dysfunction	0
sexual dysfunction	0

3.6. Correlation of Outcome at Discharge

While there was no significant difference in ICU admission between patients with complete and incomplete recovery ($p = 0.227$), deceased patients were admitted more often to the ICU than patients with compete recovery (OR = 49.9, $p = 0.0002$) and patients with incomplete recovery (OR = 30, $p = 0.001$). Further, deceased patients had higher rates of central paresis than patients with complete recovery (OR = infinity, $p = 0.041$). Patients with incomplete recovery were diagnosed less often with meningitis than patients with complete recovery (OR = 0.3, $p < 0.0001$) and more often with meningoencephalomyelitis (OR = 7, $p < 0.0001$), central paresis (OR = infinity, $p = 0.012$), peripheral paresis (OR = 19, $p < 0.0001$), cranial palsy (OR = 5.3, $p = 0.02$), and pain in extremities (OR = 12, $p = 0.002$). (Table 4).

3.7. Patients with Fatal Outcome

Patient 1 was a 39-year-old male with a kidney transplant and immunosuppression. He developed a severe diffuse CNS dysfunction (GCS = 3), needed mechanical ventilation, and died 4 weeks after the onset of TBE. The cause of death was described as extensive brain inflammatory damage and destabilization of brain functions. Patient 2 was a 47-year-old male with arterial hypertension and hyperuricemia. He had severe diffuse CNS dysfunction (GCS = 3) and died from elevated intracranial pressure 4 weeks after the onset of disease. Patient 3 was a 48-year-old female with arterial hypertension. She had

severe diffuse CNS dysfunction (GCS = 3) and a central paresis. She died 4 weeks after the onset of TBE. The cause of death was described as extensive brain inflammatory damage and destabilization of brain functions. Patient 4 was a 66-year-old male with arterial hypertension. He had a disturbance of sensibility, a paresis of the left arm, and neck muscle dysfunction. He died within 4 weeks of TBE onset, caused by respiratory insufficiency. Patient 5 was a 79-year-old female with arterial hypertension who died after 4 weeks of TBE onset. The cause of death was not recorded.

3.8. Blood and CSF Findings

No differences in blood parameters were observed when patients were grouped according to diagnosis (Figure S1). In CSF, we observed significant differences in protein concentration (M lower than ME, $p < 0.001$; M lower than MEM, $p < 0.001$) and lactate concentration (M lower than MEM, $p < 0.05$; ME lower than MEM, $p < 0.05$). There were no significant differences in leukocyte, neutrophil, and lymphocyte counts and glucose concentration (Figure S2).

3.9. Literature Review

In total, 37 clinical studies published between 1975 and 2020 were included [3,4,6,7,10,11,16–46] (Table 6). The distribution of diagnoses showed the frequency of M ranging from 7 to 78%, ME from 13 to 84%, and MEM from 3 to 11%. In children, M ranged from 63 to 97%, ME from 1.5 to 37%, and MEM from 0 to 4%. Only one study reported on MM (Table S3). The description of paresis showed a frequency of overall paresis ranging from 1.6 to 10%, overall paresis of extremities ranging from 0.7 to 15.1%, peripheral paresis of extremities ranging from 0 to 10.6%, central paresis of extremities ranging from 0.9 to 2.9%, and cranial nerve palsies ranging from 1 to 11.3% (Table S4). In total, 34 clinical studies, with a total of 35,875 patients, reported on mortality rates ranging from 0 to 6.3%, with no significant improvement over the decades. Children had significantly lower fatality rates, ranging from 0 to 0.2% (Table S5).

Table 6. Summary of results from the literature review and our study.

	Literature Review, Range (%)	EU-TICK-BO Cohort (%)
diagnoses		
meningitis	7–78	37
meningoencephalitis	13–84	49
meningoencephalomyelitis	3–11	11
meningomyelitis	0	3
pareses		
… of extremities, all	0.7–15.1	10.1
… of extremities, peripheral	0–10.6	7.4
… of extremities, central	0.9–2.9	2.3
… cranial nerve palsies	1–11.3	4.5
mortality rate	0–6.3	0.9

4. Discussion

This is the first multicenter report on clinical findings of TBE patients from six highly endemic European countries. We confirm the high rates of patients with encephalitic disease caused by TBEV in European countries, as previously described by single-center studies or national studies [3,4,16,20,34]. The analysis of patient characteristics confirmed higher age as a risk factor for severe disease, as has been shown before [4,20,24]. Older age groups had a higher risk for meningoencephalitis and meningoencephalomyelitis. Further, pre-existing comorbidities were identified as risk factors for meningoencephali-

tis and meningoencephalomyelitis. Similar to previous reports, we observed a relatively high proportion of patients with moderate (43.4%) and severe meningoencephalitis (5.8%) [34,39,47]. Additionally, a high proportion of patients with myelitis (13.1%) was seen, whereas 2.7% had myelitis without signs of encephalitis. Interestingly, case reports about MM have been published, but the literature review showed only one clinical study describing MM as a separate clinical diagnosis, [18] suggesting a likely underreporting of patients with MM. A significant proportion of patients (10.1%) developed paresis of extremities, which was consistent with previous publications suggesting a rate from 0.7% to 15.1% [7,22]. Upper extremities were predominantly affected, as shown before [8]. Interestingly, a differentiation between peripheral and central paresis was rarely described, and paresis was often summarized as limb paresis. Cranial nerve palsies were seen in 25 (4.5%) patients, which was consistent with previous publications suggesting a rate of 1% to 11.3% [7,22]. A fatal course of disease was seen in 5 (1%) patients. Previous reports show similar death rates ranging from 0 to 1.44% (Table S5). In our study, patients with a fatal course of disease were aged between 39 to 79 years. Although we observed severe cases, none of the pediatric cases died. A relatively low mortality rate in children and adolescents has been reported before [31,44,45]. According to our findings and to the findings of the literature review, no significant decrease in mortality rates during the last decades was found. The analysis of routine laboratory blood parameters showed no significant differences. However, patients with M had significantly lower CSF protein and lactate concentrations compared to patients with ME or MEM. These findings are consistent with previous studies that reported elevated CSF protein levels in patients with ME [48]. Another study found an association of high CSF protein levels with elevated rates of sequelae [5]. CSF lactate levels are generally reported to be within a normal range [48,49], while publications on patients with MEM also describe elevated CSF lactate levels [50]. More than half of the patients were discharged with incomplete recovery (176/298 patients, 59%). This included a high proportion (80/298 patients, 27%) with no expectation of complete recovery at discharge according to the clinician's assessment. Previous publications also describe high numbers of patients with sequelae after TBE infection [6,8,10,51,52]. Most impressively, TBE causes pareses of extremities in 10.1% of patients, with incomplete recovery of paresis at discharge. This impairment is a major factor for loss of function and loss of life quality and attributes to the high burden of TBE disease [53]. Follow-up studies showed persistence of pareses in more than 50% of patients one month after discharge [5,54]. Another follow-up study showed that only a few patients had a resolution of pareses within 2–7 years after discharge [52]. Further findings at discharge included a broad range of subjective symptoms (headache, decreased concentration, decreased stress tolerance) and objective signs (tremor and ataxia). A Slovenian study investigated the burden of TBE, which amounted to 3.1 disability-adjusted life years (DALYs) per TBE case [53]. In summary, TBE causes severe sequelae and quantifiable long-lasting limitations in daily life.

Our cohort included 16 patients with a history of previous TBE vaccination; 7 patients were fully vaccinated while 9 were incompletely vaccinated or missed receiving a booster vaccination according to recommendations. In contrast to previous studies, we observed a high proportion of children and adolescents with vaccination breakthrough infections [55,56]. In total, 9 of 16 vaccine breakthroughs were reported in patients younger than 20 years of age, and 7 of them were from a single center in Austria. This high proportion of children and adolescents with vaccination breakthrough infections might be the result of a special screening program of the Department of General Paediatrics, Medical University of Graz, to improve diagnostics in children with encephalitis and raise awareness for TBE breakthrough infections.

Literature about the severity of TBE breakthrough infection is inconsistent. Previous case reports and case series studies have described a more severe course of disease in patients with vaccination breakthrough infection, while a recent publication investigating a large cohort in Germany did not substantiate this finding [57,58]. The analysis of our cohort showed no significant difference in the distribution of diagnosis or in outcome at

discharge when comparing vaccinated or unvaccinated patients; however, the number of breakthrough cases was low.

Although this analysis was carried out conscientiously, there may be potential limitations. According to viral epidemiological data, in all patients with TBE infections, the European TBEV subtype was presumed, though a differentiation of European, Siberian, and Far Eastern subtypes was not made due to non-feasibility in clinical routine. Possible coinfections with borrelia were excluded at each individual center according to clinical routine. Borrelia-specific diagnostic results were neither recorded nor reviewed by the lead study center. In this study, the true incidence of sequelae of our patients remains unknown. We only recorded the outcome at discharge since standardized follow-up investigations in all patients are of limited feasibility in routine patient care. Further investigation, including a detailed follow-up protocol, will be needed to study this subject. Further, the categorization of patients with incomplete outcomes at discharge for expected recovery is subjective to the corresponding investigator and is influenced by personal experience.

5. Conclusions

This is the first international multicenter study of patients with TBE from different European countries. We observed high rates of patients with encephalitis and high rates of patients with lasting signs and symptoms at discharge. The comparison with previously published cohorts showed a likely underreporting of patients with meningomyelitis and patients with central paresis, which might be caused by different case record forms. Therefore, we suggest the use of a uniform case record form to monitor the full spectrum of disease and to raise awareness for disease prevention, particularly in countries with low vaccination rates.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/microorganisms9071420/s1, Suppl. Case Record Form (CRF), Suppl. Table S1. Patient recruitment sites, Suppl. Table S2. Distribution of paresis in patients with peripheral and central paresis of extremities, Suppl. Table S3. TBE patients assigned to M, ME, MEM, MM or other diagnosis according to 20 clinical studies from European countries published during 1975–2019., Suppl. Table S4. TBE patients with paresis according to 23 clinical studies from European countries published during 1975–2019., Suppl. Table S5. TBE Fatality rate according to clinical studies from 34 European countries published during 1975–2020., Suppl. Figure S1. Findings in blood on admission., Suppl. Figure S2. Findings in cerebrospinal fluid (CSF). Tukey plot with whiskers. * indicates $p \leq 0.05$, ** indicates $p \leq 0.005$ and *** indicates $p \leq 0.0005$.

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