ΟΙΚΟΝΟΜΙΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ATHENS UNIVERSITY OF ECONOMICS AND BUSINESS

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ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ & ΤΕΧΝΟΛΟΓΙΑΣ ΤΗΣ ΠΛΗΡΟΦΟΡΙΑΣ

ΤΜΗΜΑ ΣΤΑΤΙΣΤΙΚΗΣ

ΜΕΤΑΠΤΥΧΙΑΚΟ

ΤΙΤΛΟΣ: Ποσοστά γρίπης μεταξύ διαφορετικών ηλικιακών ομάδων στα ομοσπονδιακά κρατίδια της Γερμανίας - Στατιστική ανάλυση

ΔΗΜΗΤΡΑ ΖΙΩΓΑ

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Που υποβλήθηκε στο Τμήμα Στατιστικής

του Οικονομικού Πανεπιστημίου Αθηνών

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ABSTRACT

Dimitra Zioga

Influenza rates among different age groups in the federal states of Germany - A statistical analysis

May 2018

This thesis follows the influenza surveillance data and analysis of the German federation from 2001-2015 for understanding the patterns exhibited in each German federal state. The statistical analysis defines patterns per age group as it was expected, as well as per state. This surveillance platform follows influenza pandemic events during these years and this affect seasonal epidemic statistics. The analysis is 2-fold (exploratory analysis and model-based inference) employing conventional statistics as well as Zero Inflated Model (ZIP) and Autoregressive Conditional Poisson (ACP) models. Many of the theories related with the transmissibility between human and avian species, observation of upward trends after a pandemic and the age group specific characteristics that may be related with incomplete vaccination appear throughout this analysis. In conclusion, this valuable methodology can correlate demographic and population elements, with the actual biology of the infection and provide a roadmap for influenza surveillance and prevention.


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ΠΕΡΙΛΗΨΗ

Δήμητρα Ζιώγα

Ποσοστά γρίπης μεταξύ διαφορετικών ηλικιακών ομάδων στα ομοσπονδιακά κρατίδια της Γερμανίας - Στατιστική ανάλυση

Μάιος 2018

Η παρούσα διπλωματική εργασία παρακολουθεί τα δεδομένα επιτήρησης και ανάλυσης της γρίπης της γερμανικής ομοσπονδίας από το 2001-2015 για την κατανόηση των μοτίβων που παρατηρούνται σε κάθε γερμανικό ομοσπονδιακό κρατίδιο. Η στατιστική ανάλυση προσδιορίζει τα μοτίβα ανά ηλικιακή ομάδα όπως αναμενόταν, καθώς και ανά κρατίδιο. Αυτή η πλατφόρμα παρακολούθησης ακολουθεί τα γεγονότα πανδημίας γρίπης κατά τη διάρκεια αυτών των ετών και αυτό επηρεάζει τις στατιστικές εποχικής επιδημίας. Η ανάλυση αποτελείται από δύο μέρη (διερευνητική ανάλυση και συμπεράσματα με βάση το μοντέλο) που χρησιμοποιούν συμβατικά στατιστικά στοιχεία, καθώς επίσης μοντέλα (ZIP) και αυτοπαλίνδρομα μοντέλα Poisson (ACP). Πολλές από τις θεωρίες που σχετίζονται με τη μεταδοτικότητα μεταξύ ανθρώπων και ειδών πτηνών, η παρατήρηση των ανοδικών τάσεων μετά από μια πανδημία και τα ειδικά χαρακτηριστικά της ομάδας ηλικιών που μπορεί να σχετίζονται με τον ελλιπή εμβολιασμό εμφανίζονται σε όλη την ανάλυση. Συμπερασματικά, αυτή η πολύτιμη μεθοδολογία μπορεί να συσχετίσει τα δημογραφικά στοιχεία και τα στοιχεία του πληθυσμού, με την πραγματική βιολογία της μόλυνσης και να παρέχει έναν οδικό χάρτη για την επιτήρηση και την πρόληψη της γρίπης.


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1. Introduction

Influenza or ‘’flu’’ is a highly contagious infectious disease that attacks the human respiratory track, the nose, throat and lungs. Is caused by the influenza RNA virus and has a toll in people of all age groups. A number of influenza epidemics in the 20th century is responsible for millions of deaths worldwide. The list includes the worst epidemic in American history, the Spanish influenza outbreak that took the life of more than 500,000 people in 1918. Today influenza persists as an extremely serious infectious disease, although the mortality rates and the threat to the general population has substantially decrease. The significance as a public health threat is evident with 20000 lives lost on US alone on an annual basis. Approximately 20,000 people die of the flu in the United States every year. The influenza virus attacks the human respiratory tract, causing symptoms such as fever, headaches, fatigue, coughing, sore throat, nasal congestion, and body aches.

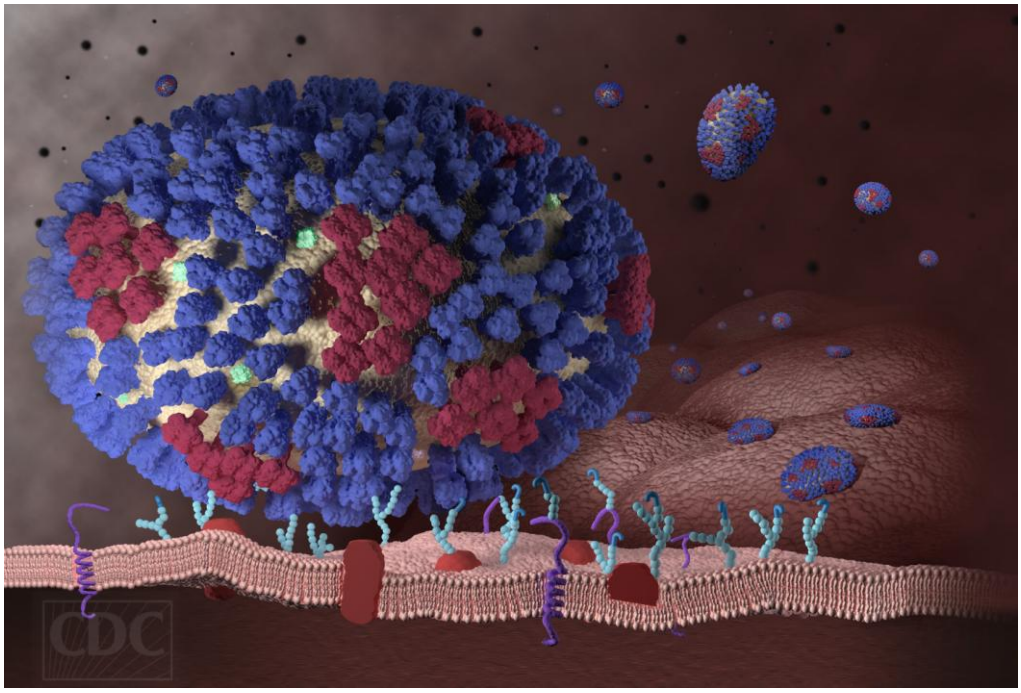


Figure 1 Understanding Influenza (Flu) Infection: An Influenza Virus Binds to a Respiratory Tract Cell https://www.cdc.gov/flu/images.htm

There are four types of influenza viruses: A, B, C and D with the first three types known to affect humans. Human influenza A and B viruses cause seasonal winter epidemics of disease (almost every winter). The emergence of novel diverse type A influenza virus can cause an influenza pandemic upon infection in humans. Influenza type C infections generally present mild respiratory illnesses and are not considered to be associated with epidemics, unlike influenza D viruses that have not been reported

to infect or cause illness symptoms to humans. influenza D viruses primer target is cattle. Influenza A virus (IAV) is an envelope form, segmented, single, negative-stranded RNA virus that belongs to the family *Orthomyxoviridae*. The waterfowl that migrates are the natural reservoirs for IAVs, but these viruses have a broad range of organisms that infect predominantly humans, domestic and wild birds, dogs, cats, dogs horses, mink and marine mammals, including seals and whales (Webster, 1992).IAVs are classified into subtypes based on two surface viral proteins hemagglutinin (H) and neuraminidase (N). There are 18 different hemagglutinin subtypes and 11 different neuraminidase subtypes. (H1 through H18 and N1 through N11 respectively). IAV can be further divided into different strains. Current subtypes of human influenza A viruses are influenza A (H1N1) and influenza A (H3N2) viruses. In the spring of 2009, a new very different influenza A (H1N1) human virus (CDC 2009 H1N1 Flu website) emerged and caused illness. This new different virus was the cause of the first influenza pandemic in more than 40 years. That virus was tagged as the "2009 H1N1", and now is the predominant H1N1 virus subtype, that circulate among humans.

Type A is considered the most virulent and is attributed for some of the most lethal pandemics in the 20th century (**Table 1).**

Table 1. Lethal influenza pandemics in the 20th century

Virus Type	Pandemic	Mortality
H1N1	Spanish flu in 1918,	20-100 million
H2N2	Asian flu in 1957	1 - 1.5 million
H3N2	Hong Kong flu in 1968	0.75 - 1 million
H5N1	Avian flu in 2004	106.000 - 396.000

There is no similar subtype classification for Influenza B viruses (IBVs) but a division exists into lineages and strains. From the current circulating influenza B viruses, two key lineages are recognized: B/Yamagata and B/Victoria. CDC has developed an international acclaimed nomenclature for influenza viruses that was accepted and communicated by WHO in 1980 Bulletin of the World Health Organization (Bulletin, 1980).

Briefly, this system employs antigenicity (A, B, C), the host of origin for non-human viruses (swine, chicken), the geographical origin (Hong Kong, Taiwan) the strain number (7, 12) the year of isolation (1968, 2009). For IAVs, as more information is available with the surface antigen proteins this is also provided.

IAVs (H1N1), (H3N2), and at least one or two IBVs are included in manufacturing each year's influenza vaccine. The exact type and ratio varies on the vaccine type. The flu vaccine protects against viruses that are either identical or share a degree of similarity to the viruses in the vaccine. The seasonal flu vaccine does not offer protection against the less prevalent influenza C viruses (ICVs). Also, this generic vaccine will not prevent infection and illness caused by other viruses or they may appear flu-like symptoms and they are spread out during the flu season.

The seasonal outbreaks predominantly occur in autumn, winter or within the early spring months. They are also termed as ''flu waves''. There are three major virus transmission paths, as they may spread 1) *directly*, through the air, when inhaling respiratory droplets produced by an infected individual during coughing or sneezing (> 500.000 virus particles are released, when a person's sneezes), 2) *through hand-to-eye, hand-to-mouth,* or *hand-to-nose* transmission. Children are more infectious than adults and can transmit the virus from just before the development of symptoms, till up to two weeks after infection, while immunocompromised individuals can shed the virus for longer time, or 3) contact with contaminated objects or surfaces IAVs can also be transmitted through contact with contaminated objects or surfaces, due to their persistence there for about fifteen minutes.

The characteristics of flu are sudden onset, high-grade fever, chills, runny nose, sore throat, cough, muscle tenderness and/or headache. Every year, many people are hospitalized and some of them die, due to flu-associated complications, such as pneumonia. People at high risk to develop serious complications, due to age, occupation, pregnancy, underlying medical conditions, immunosuppression, should be yearly vaccinated routinely, in order to prevent them. The flu can be, frequently, a reason for school and workplace abstinence.

2. Influenza epidemiology

2.1 Symptoms and Diagnosis

The influenza virus attacks the human respiratory tract, causing symptoms such as fever, headaches, fatigue, coughing, sore throat, nasal congestion, and body aches.

Table 2 presents the most common symptoms and their differences between the flu and a cold.

Table 2 Influenza and cold symptoms (according to the CDC flu website)

Flu vs Cold		
Signs and Symptoms	**Influenza**	**Cold**
Symptom onset	Abrupt	Gradual
Fever	Usual; lasts 3-4 days	Rare
Aches	Usual; often severe	Slight
Chills	Fairly common	Uncommon
Fatigue, weakness	Usual	Sometimes
Sneezing	Sometimes	Common
Stuffy nose	Sometimes	Common
Sore throat	Sometimes	Common
Chest discomfort, cough	Common; can be severe	Mild to moderate; hacking cough
Headache	Common	Rare

2.1.1 Diagnostic Methods adopted by Alison et al (Allison, 2016)

As influenza viruses target respiratory epithelium; thus procedures that sufficiently sample this site provide the best diagnostic yield, and as a result, nasopharyngeal (NP) swabs or nasal washes are more sensitive compared to less invasive throat swabs (Atmar Ral, 2011; Hayden FaP, 2009). The laboratory methods used for diagnosis are either direct or indirect immunofluorescence, viral culture, rapid antigen detection and molecular detection (Landry, 2011; Atmar Ral, 2011; Hayden FaP, 2009). **Table 3** highlights some of the key differences between these methodologies. Molecular diagnostics are not cost effective but becoming increasingly common. Based on participation data from College of American Pathology (CAP) surveys, the number of laboratories utilizing molecular methods increased from approximately 217 in 2013 to approximately 360 in 2014. Nevertheless, the use of rapid antigen tests remain the most popular according to CAP survey participation data, according to whom at least 2,205 laboratories in 2013were using them and increased to 2,900 in 2014.

Table 3 Comparison of Methods for Influenza Detection (adopted from (Allison, 2016)

Method	Sensitivity	Specificity	Potential to Detect Other Respiratory Viruses	Turnaround Time	Cost	Hands On/Expertise
Culture	High	Very high	Very High	Low	Average	Low
DFA [a]	Average	High	Average	Average	Average	Low
Antigen	Low	High	Average	Very High	Very High	Very High
Nucleic acid detection	Very High	Very High	Variable	High	Low	Variable

[a] Direct fluorescent antibody; rating scale **Low** to **Very High**, with **Very High** indicating that the method is very favorable for a particular attribute.

2.2 Prevention - Management

The best way to prevent seasonal flu and its transmission, is annual vaccination, as well as respecting hygiene rules, for example covering of the mouth with the forearm during cough and frequent hand washing.

According to the CDC recommendations, a number of vaccines are available for influenza viral infections. This list includes inactivated and recombinant influenza vaccines. These therapeutic options are available for the winter season of 2017-2018. Both trivalent (three-component) and quadrivalent (four-component) flu vaccines will be available. The vaccine is seasonal meaning that the result of the application during the flu season, directs and affects the development of more effective vaccines for the seasons to come. The traditional flu vaccine is made to protect against a major trio of viruses (thus called trivalent): the H1N1 (A virus), the H3N2 (A virus) and an influenza B virus. Trivalent flu vaccines, that consists of three different parts include:

Standard-dose trivalent shots (IIV3), that are manufactured using virus grown in eggs. with different flu shots to be approved for different age groups. Most shots are injected intramuscularly in the arm with a needle and they have different formulation or/and content according to the age group that they are addressed. For the older (>65 years) a high dose trivalent shot is given, where as a recombinant trivalent egg-free shot is preferred for adults (18-65) and pregnant women, and an alternative trivalent shot with an adjuvant immune-stimulant has been in the circulation for the >65 years bracket.

The quadrivalent flu vaccine is designed to be more diverse and therefore protecting against four different flu viruses; two influenza A viruses and two influenza B viruses. The selection of the second B virus was not straightforward, as two very different B viral lineages have circulated in the general population.

The quadrivalent flu vaccines provide more options as they are approved for administration to a broader age bracket including 6 year old kids, an intradermal (ID) variety for the general population (18-65) to skip the IM delivery with a smaller needle, a flu shot that contains virus growing in cell culture (4 years or older) and the recombinant shot for the broader population (18-65).

Infection Control

Reasonably effective ways to reduce the transmission of influenza include good personal health and hygiene habits such as 1) avoiding contact with eyes, nose or mouth, 2) frequent hand washing with soap and water, or with alcohol-based hand rubs, 3) covering the mouth and nose, while coughing and sneeze, using the forearm. Other effective measures to prevent spread and infection is the reduction of visits in crowded places during an outbreak, the avoidance of close contact with sick people and staying at home, if infected. Although face masks might help prevent transmission, there is mixed evidence on the beneficial effects in the community. Smoking raises the risk of contracting influenza, as well as producing more severe disease symptoms.

Since influenza spreads through both aerosols and contact with contaminated surfaces, surface sanitizing may help prevent some infections. Alcohol is an effective sanitizer against influenza viruses, while quaternary ammonium compounds can be used with alcohol, so that the sanitizing effect lasts longer. In hospitals, quaternary ammonium compounds and bleach are used to sanitize rooms or equipment that have been used in by or during the care of patients with influenza symptoms. At home, this can be done effectively with a diluted chlorine bleach.

Social distancing strategies used during past pandemics, such as closing schools, churches and theaters, slowed the spread of the virus but did not have a large effect on the overall death rate. It is uncertain if reducing public gatherings, by for example closing schools and workplaces, will reduce transmission since people with influenza may just be moved from one area to another; such measures would also be difficult to enforce and might be unpopular. When small numbers of people are infected, isolating the sick might reduce the risk of transmission.

2.3 Flu Complications

The majority of the flu infected individuals will recover in a timeframe of days and no more than two weeks. A number of people may develop complications as the aftermath of flu with more characteristic the example of pneumonia. Occasionally, flu complications may escalade in life threatening conditions that vary on the infected individual and may lead to death. The list of complications besides pneumonia includes bronchitis sinus and ear infection. Chronic health conditions will most probably worsen by a flu infection. Flue triggers for example asthma complications or chronic congestive heart failure.

2.4 Influenza therapeutics

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

A number of antiviral medications target influenza viruses have been proven a crucial adjunct to influenza vaccines for the effective management and control of influenza infections. This list includes 5 available, FDA approved, prescribed antiviral drugs that they either treat or prevent influenza:

Oseltamivir (oral administration, available as a generic version or under the name Tamiflu®),

Zanamivir (Relenza®) inhalatory,

Peramivir (Rapivab®) intravenous.

These drugs are chemically related antivirals as they share the same target (neuraminidase inhibition) and have been found against both influenza A and B viruses.

Oseltamivir was approved by the FDA and became available at the end of 2016. Amantadine and rimantadine are antivirals belong in the class of adamantanes. The latest two medications are active against influenza A, but share no activity for influenza B viruses. Amantadines present site effects that have been a potential limitation to their use. Nausea, dizziness and insomnia, have been reported as the most common adverse effects from their use.

3. Influenza Surveillance

The health toll of influenza remains high through the years and a major public concern. Although there is a variation, it can be estimated with certainty that it causes 3-5 million cases of severe illnesses that resulted in 250–500 thousand deaths annually around the world (WHO, 2009). The pandemics that occur for the rise of a new antigenic subtype from time to time, especially for the last 100 years that a reasonable tracking system exist, will spread for person to person raising a new red alert. The epidemics will keep up occurring on a constant annual basis, leaving a considerable portion of the public constantly susceptible as a result of the virus A evolution that leads in the evasion of human immunity. Temperature, as it was mentioned so crucial for the occurrence of the epidemics, with the low winter temperatures to be dominant for these events with the exception of regions in the tropics. For many countries, traditional sentinel surveillance systems exist that trace and track influenza-like illness (ILI) occurrence and the prevalence of PCR-confirmed influenza samples among tested specimens. The product of these quantities has been proposed as a proxy for the incidence of influenza, up to an unknown multiplicative constant, under certain assumptions (Goldstein, 2011).

CDC has a comprehensive collection of ILI weekly surveillance data that were gathered routinely for over 3 decades. At the same time a number of algorithms have been developed to foster the estimation for ILI based on online search queries (Ginsberg, 2009); the Google Flu Trends (GFT) real time ILI data are now available in 29 countries around the globe. The surveillance data have actual value to assess the activity of the virus in the general population, but at the same time such measures typically do not reflect the actual influenza infection rates. For example, the ILI is determined through the number of patients that would be diagnosed with the infection during the visit to the physician in US but this is rather limited for the sick non diagnosed. In addition, the underreporting occurs commonly due to asymptomatic infections and a substantial number of symptomatic but unattended. These monitoring pitfalls, taken together with other monitoring errors, create a number of challenges for highlighting the complete picture for the influenza epidemiologic basis utilizing these data.

To cover this gap, Bayesian inference methods have been developed and exist. When these methods would be coupled with dynamical models, they can offer accurate approximations to these data and partially translate dynamical systems (Shaman, 2012). The work of including previous publication (WELCH, 2011) focuses in the application of Bayesian inference frameworks (also known as data assimilation methods) that essentially simulate seasonal outbreaks and demonstrated that there is a possibility to make reliable predictions of the peak timing of seasonal influenza employing GFT ILI data combined with regional isolation data of viral influenza (called and ILI+) (Shaman, 2012). By using the same inference methods the researchers were able to estimate key epidemiological parameters for both pandemic and seasonal outbreaks, employing the total number of outbreaks in 115 major US cities from the 2003–2004 through 2012–2013 influenza seasons, and demonstrate how big-data-driven surveillance can be valuable to reveal the transmission dynamics of influenza among the general population.

Annual influenza epidemics significantly burden health care. The anticipation of a influenza epidemics has the marginal advantage of timely preparation. A recent survey from the Belgian Scientific Institute of Public Health (WIV-ISP) monitors both influenza and influenza-like illnesses (ILIs) incidences and provides reports on a weekly basis (Michiels, 2017). The system is electronically organized in a such a form that allows general practitioners and specialized physicians that works in out-of-hour cooperatives (OOH GPCs) to register ILIs diagnosis. This accessible electronic system that constitutes these records (EHR) appears as an interesting working tool. EHR was recently identified as a core of exploring two objectives the putative value of EHR to model seasonal influenza epidemics in combination with ILI data from the OOH GPC Deurne-Borgerhout, Belgium as well as to assess the quality of these data for the accurate prediction of potential new epidemics that ultimately will strengthen the national influenza surveillance by WIV-ISP.

The methodology included assessment of the validity for the OOH GPC data set with a direct comparison of OOH GPC ILI data with WIV-ISP ILI data for the time period 2003-2012 and by employing Pearson's correlation. The best fitting prediction model employing the OOH GPC data that was developed on 2003-2012 data was further validated on the 2012-2015 data. This model was further compared with other commonly used and well established. This analysis performed, formulated an 1-week and one-season ahead prediction. In the OOH GPC, 72,792 contacts were recorded from 2003 to 2012 and a total number of 31,844 for the time period from 2012 to

2015. The mean ILI diagnosis/week was calculated in 4.77 (Interquartile Range, IQR, 3.00) and 3.44 (IQR 3.00) for the two time periods selected respectively.

The correlation among OOHs and WIV-ISP ILI incidence was calculated high ranging from 0.83 up to 0.97. The addition of a secular trend (or otherwise a 5 year cycle) and the use of an first-order autoregressive modeling accounting for the epidemic component in coordination with the use of Poisson likelihood yielded the best predictive results. The selected model was capable for the best 1-week ahead prediction performance when compared to the existing surveillance methods. There was less accuracy prediction for the starting week of the epidemic (±3 weeks), fact that didn't apply for the predicted duration of the next season.

In conclusion, the OOH GPC data are amenable for extensive use to predict influenza epidemics both in accuracy and in speed for 1-week and one-season ahead. There is also a plausible complementary use for the national influenza surveillance systems that will facilitate optimal preparation upon epidemic anticipation.

3.1 Surveillance of influenza in Germany

The impact of influenza pandemics have been enumerated and evaluated extensively in Germany (Buchholz, 2016). Analysis of the literature and the available data sets has revealed that dissection of 4 pandemics and calculation based on monthly and weekly all dead statistics provide 426,600 (1918-1919), 29,100 (1957-1958), 46,900 (1968-1970) and 350 (2009) excess pandemic-related deaths. There also determination of excess mortality ranging between For 691 per 100,000 (0.69 % in 1918-1919) and 0.43 per 100,000 (0.00043 % in 2009). These numbers are not very different for the pandemic mortality calculations and estimations globally.

The available influenza surveillance systems in Germany include the one based on information from the Robert Koch Institute (RKI) that incorporates primarily data of the national sentinel system of the "Working Group Influenza" (Arbeitsgemeinschaft Influenza) that enlist reports of primary care physicians about patients with acute respiratory illnesses and results of laboratory tests of respiratory samples taken from patients with influenza-like illness. The virological lab results are supplemented by data from the state laboratories of Baden-Wuerttemberg, Bavaria, Mecklenburg-Western Pomerania, Saxony, Saxony-Anhalt and Thuringia. The mandatory reports of laboratory confirmed influenza submitted by county health departments via state health departments to RKI were analyzed as well as results from the internet based »GrippeWeb« surveillance of syndromic reporting from the general population about the individual occurrence of acute respiratory illnesses. This analysis is more structured and intuitive but less thorough than the generic respiratory infections control and prevention system that calculates the number of positive infectious disease diagnoses (pathogens / people affected), that are reported and published, according to the federal legislation. The Public Health local services collect data with influenza patient-identifier elements including age, sex, weight, medical treatment and details on residence.

Depending on the most serious influenza outbreak, we have registered the specific year with the corresponding federal state and we have check (monitored) the patients, so we can identify specifically the etiology behind distinct increase of flu patients.

In 2001, the surveillance system for diseases that require notification was standardized in Germany through establishing the Protection against Infection Act (*Infektionsschutzgesetz: IfSG*) ((2000)). This resulted to a direct implementation of an electronic surveillance system to monitor infectious diseases outbreaks within the national public health institute in Germany, the Robert Koch Institute (RKI). This model system was embedded within the case-based electronic surveillance system SurvNet@RKI (Faensen, 2006). This effort and others made clear that a comprehensive, electronic surveillance system was absolutely necessary. This in fact prompted parallel efforts in Germany as well as other countries to establish similar reporting systems (Gómez-Outes, 2012).

RKI has provided in detail analyses for recent influenza epidemics (RKI, 2016). Among samples of the sentinel the first case was laboratory confirmed in calendar week (CW) 41/2015. Laboratory confirmed influenza was detected since CW 46 continuously and the proportion of positive samples (positivity rate) increased substantially in CW 2/2016. The positivity rate is one relatively consistent indicator for the determination of the Germany influenza season time frame. The positivity rate is an indicator for the determination of the beginning and the influenza season end in Germany. Acute respiratory diseases activity that happens in the sentinel practices and had surpassed the low background threshold activity in CW 1/2016, reaching maximum level between CW 7 and 11/2016. Despite this observed activity, these values still remained significantly lower when compared with the observed 2014/15 and 2012/13 peak week observations. During the influenza epidemic, the influenza-associated consultations (estimated influenza consultations vs. the expected without influenza) were in excess and specifically was 4/100 000 (95 % confidence interval (CI) 3 500 000 – 4 500 000). The calculated estimate for the number of influenza-associated sick certificates (reflects the number of patients in certified healthcare need and in fact is fundamental for infants and children, that will not get a certified leave of absence) was defined in 2 200 000 (95 % CI 1 900 000 – 2 500 000) and the estimation for the infected that were held in the hospital for treatment was 16 000 (95 % CI 13 000 – 19 000). All these estimated numbers were lower when compared with the intense influenza seasons 2012/13 and 2014/15 but significantly in contrast with the mild 2013/14 season. Direct comparison with the season 2014/15, reveals less number of severe cases that were observed in the oldest age group (≥ 60 years).

As the epidemic started, the circulating influenza A(H1N1)pdm09 viruses had a huge toll in the younger fraction of the general population. The 2015/16 season, was also characterized from an atypical spatial distribution with respect to the influenza activity with increasing observed levels from east to west. The molecular characterization by the National Reference Center for Influenza (NIC), identified Influenza B at a 55 % for all the respiratory samples with a positive preliminary result, 43 % for A(H1N1) pdm09 followed as a close second. There was also a sporadic and limited presence for Influenza A(H3N2) viruses that were circulated at 2 % sporadically. During the next season (2015/16) the majority of the A(H1N1) pdm09 viruses had antigenically similar features in alignment to the vaccine virus A/California/7/2009. However, the undisputed majority (96 %) of the identified as influenza B viruses were members of the Victoria lineage. Notably, that season, this B-lineage was not a part of the trivalent influenza vaccine. A number of influenza viruses were tested for antiviral efficacy by the NIC and none was even remotely sensitive to either oseltamivir or zanamivir. Additional information is gathered by additional surveillance systems especially during the hype of the infection seasons. For example the results available from the internet platforms such GrippeWeb are in agreement and they exhibit good correlation between the Medically Attended Acute Respiratory Infection (MAARI) numbers from GrippeWeb and the Arbeitsgemeinschaft Influenza supporting the accuracy of the estimates in both systems. According to a number of pilot studies from GrippeWeb Plus, in the swabs that obtained from a subgroup of participants, through self-administered sampling, respiratory viruses were identified in 72 % of samples from patients that were symptomatic. The data from a new syndromic sentinel hospital system (»ICOSARI«), that uses a case-based, ICD-10- coded information present the analysis of severe acute respiratory infections (SAARI) in within the hospital patients grouped by age in three recent seasons.

4. Methodology

(adapted by http://soc-research.info/quantitative_eng/7.html)

4.1 Data

Structure of the German surveillance system that was utilized: In Germany, the "Act on the Prevention and Control of Infectious Diseases "

(Infektionsschutzgesetz – IfSG) defines infectious diseases and specifies positive diagnoses of pathogens according to federal legislation. The act also explicates two separate paths of notification:

1. The local health public departments are notified for diseases and pathogens. It is the responsibility of the local authorities to exhaustively investigate on a case by case basis and tracing potential contacts related with these infections. When an epidemiological connection is established the notification data are connected on a different level For every occasion and notification that qualifies as a case for the RKI the anonymity of the data is sustained and the subsequent transfer between the corresponding federal state health department to RKI.

2. There are occasions, where pathogens and infections are notified directly to RKI depending on specific case criteria are met. Pathogens are notified to the RKI directly, where they are evaluated according to specific case criteria. Data collected under provisions (1) and (2) are analyzed and periodically they are included in a detailed publication by the RKI Department for Infectious Disease Epidemiology.

There are also specific state regulation for reporting a number of diseases and pathogens Bavaria, Berlin, Brandenburg, Hessen, Mecklenburg-W, Rhineland-Palatinate, Saarland, Saxony, Saxony-Anhalt and Thuringia) only. In this occasion even the case definition is altered for a number of diseases and they often published in the *Epidemiological Bulletin 5/2009.* In the database Surv*S*tat@RKI2.0, data related with these specific diseases that are reported locally and regionally can be retrieved by making the appropriate word selections (eg. "via local and state health department") and setting the appropriate filter that matches with under the investigation attribute and regulation to <according to state specific regulations>.

The data update happens on a weekly basis and this update involves both diseases and pathogens reported via local and state health departments or occasionally on a monthly basis (for diseases/pathogens notified directly to RKI) and this is

synchronized with the reference date that are deployed for publication in the *Epidemiological Bulletin.* These **datasets status** is time and quality different for the two notification paths thus is displayed separately, with the respective reporting period added in parentheses.

There is detailed information available on the causative **pathogen** and can be obtained for most of the diseases. For a number of diseases with an excessive number of defined pathogen subtypes or subspecies, these are subsumed to wider subcategories.

Place: Cases reported through the local and state health departments, inserted in the notification system are allocated by the local health department county which files the case (most often at the residence of the case person). For the cases reported directly to RKI the allocation occurs by the residence first three digits of the five digit postal code. There are different filters and levels to display the reported cases either by **Federal state** or **Territorial Unit** (NUTS Level 2) or **County**. For the cases reported directly to RKI the lowest level, called **Region** subdivides each territorial unit between larger cities and the rural region. For the interpretation of the data it should be considered that the localization of cases only reveals the place of residence of the case related persons. Information about the place of infection is not available in SurvStat@RKI 2.0.

The recommendation for the comparison between different diseases frequencies in the available classes of regions (state, territorial unit or county/region) is using **incidence** assessed in cases / 100,000 inhabitants/ time period) where as the case numbers, are a working measure to calculate differences within the population. The same measure also applies for direct comparisons between different age groups and/or sexes. As it is possible, a simple spike of 1 or 2 cases to lead in big measurable incidence in low population group differences is suggested to follow thoroughly always both the absolute case numbers and incidence. For example when the measured and reported Incidences <0.01, there is always rounding to 0.00. The total **incidence** calculated, refers to the entire period selected from the "Filter Settings" segment unless a time period is specified, for example let's say that somebody calculate incidence for the entire reporting period since 2011. This was common in the earlier SurvStat versions where incidence was calculated for a time period of several years. SurvStat@RKI 2.0, provides the option to obtain the mean

incidence by dividing by dividing the total incidence for a number of years by the relevant number of years selected in the specific query.

The population data necessary for the incidence calculation is provided by the states' statistical offices and updated regularly. To calculate the incidence for a time period covering several calendar years, SurvStat@RKI 2.0 computes an average population from the population data of the relevant years.

SurvStat@RKI 2.0 carries modified and updated time variables that have been embedded and they are readily available. The new attributes **season week** and **season year** come both in two variations, under the names (27) and (40). The **season year** (27) initiates from the 27th calendar week and ends with the 26th week of the following calendar year. Thus, the first **season week** (27) is defined as the 27th week of the calendar year. This provides a more comprehensive view and assist the display for seasonal infectious diseases that present lowest case numbers lowest case numbers in the middle of the calendar year (for example norovirus or gastroenteritis-presenting infections). Season week (27) will be used as the key attribute for column display of the table that carries the results. This variable shifts the time-axis by 26 weeks, affecting the resulting diagram that in order to display the disease seasonality where the total phenomenon will also be in full display with an uninterrupted rise, maximum and fall a far as it concerns case numbers. In the case of influenza where the highest case numbers are reported in the first quarter of the year a different **season week (40)** is recommended for a more relevant and detailed display. The option to filter the off season weeks by the deselection in the "Filter Settings" section in the query form. This will narrow down data vision to a time span for the on season influenza season for example (calendar week 40 to week 20 of the following year).

Data collection We primarily collect patient data from SurvStat@RKI2.0

Höhle, Michael; Riebler, Andrea (2005) : The R-Package surveillance, Discussion paper // Sonderforschungsbereich 386 der Ludwig-Maximilians-Universität München, No. 422, (cases per 100,000 inhabitants per time period) from a number of different federal Germany states from 2000 until 2015. These regions include Baden-Wurttemberg, Bavaria, Berlin, Brandenburg, Bremen, Hamburg, Hessen,

Mecklenburg-Vorpommern, Lower Saxony, North Rhine-Westphalia, Rhineland-Palatinate, Saarland, Saxony, Saxony-Anhalt, Schleswig-Holstein and Thuringia.

Software The RStudio, SPSS, and the GraphPad Prism (Version 7) were used for data analysis, and plotting.

Statistics Values are means of three separate experiments and bars are SEM. Differences between means were tested for significance by one-way ANOVA (R Studio / SPSS). The significance level was set at $P < 0.05$.

4.2 Models

Zero Inflated Model

(adapted by SAS/ETS(R) 13.1 User's Guide and wiki/Zero-inflated model)

Zero-Inflated Count Regression Overview

A **zero-inflated model** is a model employed in statistical analysis that is based on the probability distribution zero-inflated, for example, a distribution that permits for frequent zero-valued observations. The first zero-inflated model is the zero-inflated Poisson distribution-based model, that focuses on a random event that contains excess zero-count data assessed when time applies as the unit (Lambert, 1992). As a typical real life example, the number of insurance claims within a given population and for a specific type of risk would be zero-inflated by this faction of the people who have not include in their policies insurance against the risk and thus are unable to claim. The zero-inflated Poisson (ZIP) model employs two basic components corresponding to two zero generating processes. The result of a Bernoulli trial is used to determine which of the two processes is used. For observation i, ***Process 1*** is chosen with probability φ_i and ***Process 2*** with probability $1-\varphi_i$. Process 1 generates only zero counts. Process 2 generates counts from either a Poisson or a negative binomial model. In general,

$$y_i \sim \begin{cases} 0 & \text{with probability} \quad \varphi_i \\ g(y_i) & \text{with probability} \quad 1-\varphi_i \end{cases}$$

Therefore, the probability of $\{Y_i = y_i\}$ can be described as

$$\begin{aligned} P(y_i = 0|\mathbf{x}_i) &= \varphi_i + (1-\varphi_i)g(0) \\ P(y_i|\mathbf{x}_i) &= (1-\varphi_i)g(y_i), \quad y_i > 0 \end{aligned}$$

where $g(y_i)$ follows either the Poisson or the negative binomial distribution.

When the probability φ_i depends on the characteristics of observation i, φ_i is expressed as a function of $\mathbf{z}_i'\boldsymbol{\gamma}$, where $\mathbf{z}_i'$ is the $1 \times (q+1)$ vector of zero-inflation covariates and $\boldsymbol{\gamma}$ is the $(q+1) \times 1$ vector of zero-inflation coefficients to be estimated. (The zero-inflation intercept is γ_0; the coefficients for the q zero-inflation covariates are $\gamma_1, \ldots, \gamma_q$)

The function F that relates the product $\mathbf{z}_i'\boldsymbol{\gamma}$ (which is a scalar) to the probability φ_i is called the zero-inflation link function,

$$\varphi_i = F_i = F(\mathbf{z}_i'\boldsymbol{\gamma})$$

In the zero-inflated Poisson (ZIP) regression model, the data generation process as it was briefly described

$$g(y_i) = \frac{\exp(-\mu_i)\mu_i^{y_i}}{y_i!}$$

where $\mu_i = e^{\mathbf{x}_i'\boldsymbol{\beta}}$.

Thus the ZIP model is defined as

$$\begin{aligned} P(y_i = 0|\mathbf{x}_i, \mathbf{z}_i) &= F_i + (1 - F_i)\exp(-\mu_i) \\ P(y_i|\mathbf{x}_i, \mathbf{z}_i) &= (1 - F_i)\frac{\exp(-\mu_i)\mu_i^{y_i}}{y_i!}, \quad y_i > 0 \end{aligned}$$

The conditional expectation and conditional variance of y_i are given by

$$E(y_i|\mathbf{x}_i, \mathbf{z}_i) = \mu_i(1 - F_i)$$
$$V(y_i|\mathbf{x}_i, \mathbf{z}_i) = E(y_i|\mathbf{x}_i, \mathbf{z}_i)(1 + \mu_i F_i)$$

Note that the ZIP model (as well as the ZINB model) exhibits overdispersion because $V(y_i|\mathbf{x}_i, \mathbf{z}_i) > E(y_i|\mathbf{x}_i, \mathbf{z}_i)$.

In general, the log-likelihood function of the ZIP model is

$$\mathscr{L} = \sum_{i=1}^{N} w_i \ln\left[P(y_i|\mathbf{x}_i, \mathbf{z}_i)\right]$$

After a specific link function (either logistic or standard normal) for the probability φ_i is chosen, it is possible to write the exact expressions for the log-likelihood function and the gradient.

Autoregressive Conditional Poisson Models (employ elements from (Ghahramania, 2009)

The Autoregressive Conditional Poisson (CAR or ACP) models are following observations are they are initially developed by Heinen in 2003 (Heinen, 2003). These models have as basic characteristic that they handle observations and data with discreteness. They attempt to address over-dispersion and place a special emphasis in serial correlation in data-series. There are many variations of these models in numerous applications, estimations can be made using maximum likelihood techniques and the easily incorporation of explanatory variables is easy (Holloway, 2010).

It is important to state, that the ACP models have been gradually developed on the need to process phenomenically complex financial volatile time data series, including returns on stocks and stock options, returns based on foreign exchange rates, that vary due to time. These observations were firstly made by the analysis of Nicholls and Quinn (Nicholls, 1982) and Engle with all his colleagues but predominantly his work with González-Rivera (1991) (Engle, 1991; Engle, 1982). These observations gradually led in the development of the Random Coefficient Autoregressive (RCA) models by Nicholls and Quinn (Nicholls, 1982), the Autoregressive Conditional Heteroscedastic (ARCH) model (Engle, 1982). At the same time a specialized platform including the Generalized Autoregressive Conditional Heteroscedastic (ARCH) and (GARCH) models (Bollerslev, 1986) have provided a more convenient framework for the study of the volatility stemming from time in financial and economic-driven observations. This has become a matter of continuous interest and dissect the high impact components of GARCH models (Thavaneswaran, 2009). This line of research is directly related with the ACP models. The issues of discreteness, overdispersion and autocorrelation are further analyzed to address modern and post modern financial issues with extensive transformations that compile both auto regression model families.

Spatial Data as a Gaussian Random Field Model

http://mc-stan.org/documentation/case-studies/IAR_Stan.html

When data are presented with a spatio-temporal structure and when observations from proximal (or neighboring regions) demonstrate higher correlation than observations

between distant regions, this correlation can be attributed for using the class of spatial models called “CAR” models (Conditional Auto-Regressive) introduced by Besag and collaborators (Besag, 1991) .

A full mathematical articulation and description has been provided through years and let in the development of ACP models (According to The following math and its notation is taken from “Gaussian Random Field Models for Spatial Data” by Murali Haran, which is Chapter 18 of the “Handbook of Markov Chain Monte Carlo”).

For the first time, it has been shown by Besag in 1974 (Besag, 1974) that encoding for the proximal relations among spatial regions (in a similar fashion with a lattice), in addition to acquiring as well as adjusting results from the lattice systems physics of particles and the Hammersly-Clifford theorem provide an equivalent distribution. This distribution between the local specification of the conditional distribution for each particle given the proximal (neighboring) particles as well as the global specification of the joint distribution of all particles. This specification of the joint distribution *via* the local specification of the conditional distributions of the individual variables is defined as a Markov random field specification.

Therefore, for a given set of observations that were taken at *n* different sub regions of a region with a number of dimensions *D* (for spatio-temporal data, the number of dimensions is usually between 1 and 4, for example, 1-3 spatial dimensions and 1 time dimension), spatial interactions between regions n_i and n_j can be modeled conditionally as a spatial random variable *w* as follows:

- Let $\boldsymbol{\omega}_{-i}$ denote the *n*- length vector $\boldsymbol{\omega}$ excluding $\boldsymbol{\omega}_i$.
- We model each $\boldsymbol{\omega}_i$ in terms of its full conditional distribution which is its distribution given the remaining random variables, w_{-i}:

$$\boldsymbol{\omega}_i \mid \mathbf{w}_{-i}, \Theta \sim \mathbf{N} \left(\sum_{j=0}^{\eta} \mathbf{c}_{ij}\boldsymbol{\omega}_j, \boldsymbol{\kappa}_i^{-1} \right) \quad \mathbf{i}=\mathbf{1},\ldots,\mathbf{n}$$

where c_{ij} describes the neighborhood structure such that c*ij* is nonzero only if *i* and *j* are neighbors and κ is the precision (inverse variance) parameter.

CAR Models

The neighborhood structure of the κ and c_{ij} elements can be stored in an $n \times n \times n$ matrix Q where the diagonal elements represent each of the n sub regions with value κ_i and the off-diagonal elements contain $-\kappa_i c_{ij}$ if subregions i and j are adjacent and 0 otherwise. Usually a common precision parameter τ, is assumed, where $\kappa_i = = \tau$ for all i.

When the matrix Q is symmetric and positive definite, this specifies a valid joint distribution,

$$\boldsymbol{\omega|\Theta \sim N(0, Q^{-1})}$$

with Θ the vector of the precision parameters. This provides a proper prior for a CAR model. However evaluation of ω requires computing the covariance matrix Q^{-1}, which is computationally expensive for large values of n.

CAR priors for spatial random effects

Conditional autoregressive (CAR) models are popular as prior distributions for spatial random effects with areal spatial data. If we have a random quantity $\phi = (\phi 1, \phi 2, ..., \phi n)'$ at n areal locations, the CAR model is often expressed via full conditional distributions:

$$\boldsymbol{\phi i|\phi j,} \qquad \boldsymbol{j \neq i \sim N} \qquad \left(\alpha \sum_{j=0}^{n} b_{ij}\phi_j, \tau_i^{-1} \right)$$

τ_i a spatially varying precision parameter, and $bii=0$

By Brook's Lemma, the joint distribution of ϕ is then:

$$\boldsymbol{\phi \sim N(0, [D\tau(I - \alpha B)]^{-1})}$$

By the following assumptions:

- $D\tau = \tau D$
- $D = \text{diag}(mi)$ an $n \times n$ diagonal matrix with m_i = the number of neighbors for location i
- *I:* an $n \times n$ identity matrix
- α: a parameter that controls spatial dependence ($\alpha = 0$ implies spatial independence and $\alpha = 1$ collapses to an *intrinsic conditional autoregressive* (IAR) specification)

- $B=D^{-1}W$: the scaled adjacency matrix
- W: the adjacency matrix ($\omega_i=0$, if i is a neighbor of j, and $\omega_{ij}=0$ otherwise)

then the CAR prior specification simplifies to:

$$\boldsymbol{\phi \sim N(0,[\tau(D-\alpha W)]^{-1})}$$

The α parameter ensures propriety of the joint distribution of ϕ as long as $|\alpha|<1|$ (Gelfand, 2003) However, α is often taken as 1, leading to the IAR specification which creates a singular precision matrix and an improper prior distribution.

A Poisson specification

With the hypothesis that data from counts have been accumulated $y_1,y_2,...,y_n$ at a number of n locations, and is anticipated that the neighboring locations will have similar counts. With a Poisson likelihood:

$$\boldsymbol{y_i \sim Poisson\ (exp\ (X_i\beta+\phi_i+log(offset}i\boldsymbol{)})$$

X_i is a design vector (the i^{th} row from a design matrix),

β is a vector of coefficients,

ϕ_i is a spatial adjustment, and log(offset$i$)accounts for differences in expected values or exposures at the spatial units (popular choices include area for physical processes, or population size for disease applications).

If we specify a proper CAR prior for ϕ, then we have that $\phi \sim N(0,[\tau(D-\alpha W)]^{-1})$ where $\tau(D-\alpha W)$ is the precision matrix Σ^{-1}. A complete Bayesian specification would include priors for the remaining parameters α, τ, and β, such that our posterior distribution is:

$$\boldsymbol{p(\phi,\beta,\alpha,\tau|y) \propto p(y|\beta,\phi)p(\phi|\alpha,\tau)p(\alpha)p(\tau)p(\beta)}$$

5. Results

5.1. Exploratory analysis

The first part of the approach was to identify the distribution and the significance of data curated per federal state per year. **Fig. 1** illustrates a box-plot with the influenza infection rates in respective German federal states through the years 2000-2015 as they become available through the RKI surveillance resources. The key observation is that influenza infection rates appear higher in Bavaria and Saxony, thus the virus affects more inhabitants independent of age in this states. The lower infection rates also correlate with less populated states including Hessen and Saarland, with the lowest rates observed in Hessen.

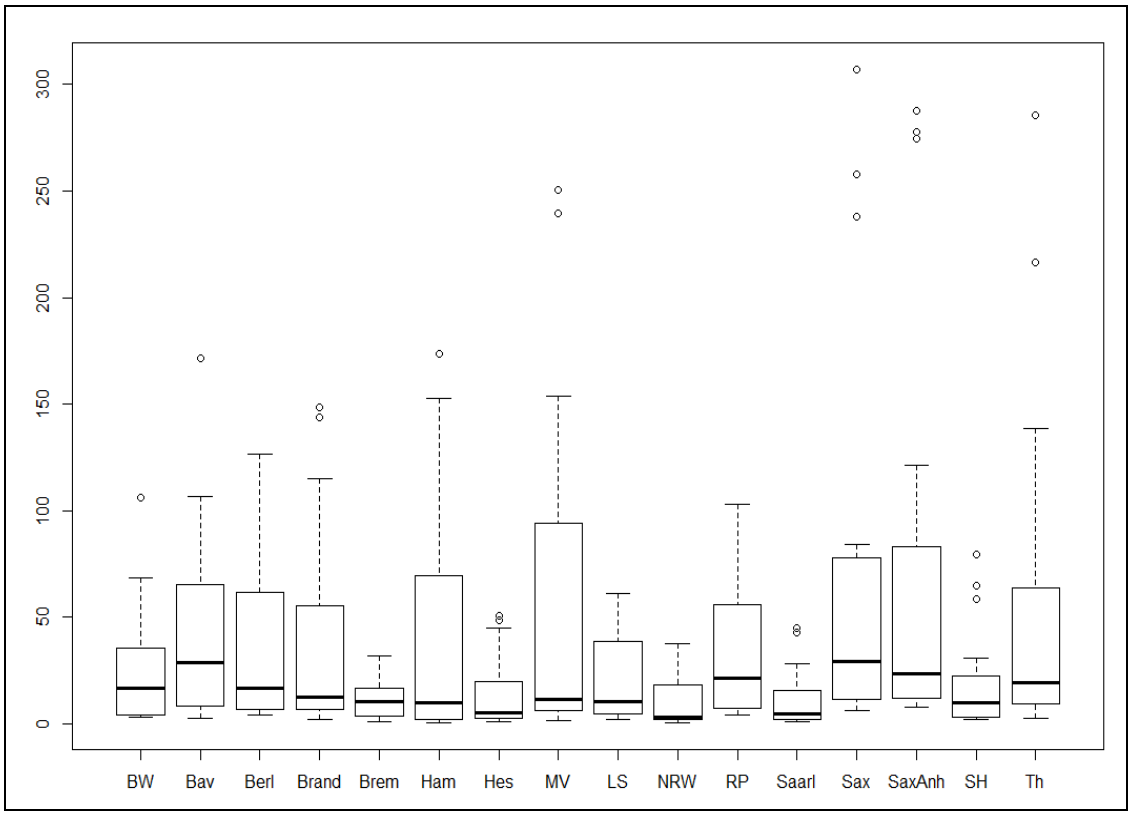


Figure 2. Box plot of influenza infection rates for German federal states from 2000-2015. Data were from the case-based electronic surveillance system SurvNet@RKI

Table 4 Descriptive influenza data in 2014 for all federal states. The table presents the basic descriptive measures of the number of patients (per 100,000 inhabitants) with influenza for all German federal states collectively (minimum, median and first and third quartile).

min	*1st Qu.*	*Median*	*mean*	*3rd Qu.*	*max*
10.45	49.49	104.60	123.90	158.15	307.16

Table 4 places emphasis in the brief cumulative all state available data of influenza patients in 2014. It is observed an 123.90 (per 100,000 inhabitants) average number of patients. The minimum number of patients was reported as 10.45 in the state of Bremen. What we deserve to comment on the year 2014, is that the average number of patients was 123.90 (per 100,000 inhabitants). The lowest number of patients was 10.45 (specifically in the state of Bremen) whereas the highest number of patients observed was 307.16 (specifically in the state of Saxony).

Table 5 Descriptive influenza data within all the RKI reporting German regions from 2000 to 2015:

State	*min*	*1stQu.*	*median*	*mean*	*3rd Qu.*	*Max*
Baden-Württemberg	**3.200**	**4.408**	**16.720**	**26.060**	**34.460**	**106.100**
Bavaria	**2.600**	**8.468**	**28.600**	**43.310**	**62.290**	**171.600**
Berlin	**4.240**	**6.978**	**16.870**	**36.160**	**49.970**	**126.600**
Brandenburg	**1.870**	**7.505**	**12.600**	**39.280**	**43.100**	**148.600**
Bremen	**0.760**	**3.405**	**10.450**	**12.080**	**16.500**	**31.790**
Hamburg	**0.40**	**2.07**	**9.81**	**40.77**	**44.52**	**173.40**
Hessen	**1.10**	**2.90**	**4.92**	**14.29**	**17.66**	**50.75**
Mecklenburg-Vorpommern	**1.260**	**7.248**	**11.390**	**59.610**	**69.780**	**250.700**
Lower Saxony	**1.86**	**4.83**	**10.64**	**21.83**	**34.74**	**61.29**
North_Rhine_Westphalia	**0.610**	**1.870**	**2.955**	**11.170**	**13.750**	**37.710**
Rhineland-Palatinate	**4.270**	**7.432**	**21.460**	**35.040**	**52.870**	**103.100**
Saarland	**0.97**	**2.00**	**4.48**	**11.44**	**14.30**	**45.11**
Saxony	**6.14**	**11.68**	**29.35**	**74.82**	**75.05**	**307.20**
Saxony-Anhalt	**7.69**	**12.05**	**23.54**	**75.30**	**64.15**	**287.60**
Schleswig-Holstein	**1.910**	**3.355**	**10.070**	**19.920**	**18.290**	**79.420**
Thuringia	**2.47**	**10.16**	**19.53**	**57.83**	**59.44**	**285.60**

Table 5 presents the basic descriptive measures of the number of patients (per 100,000 inhabitants) with Influenza and cover each German federal state that reports in the RKI system separately (these metrics include minimum, median, mean, maximum, as well as assessments in the first and third quartile). A common feature that can be noticed at a glance, is that data for every state exhibit strong positive asymmetry (the average is higher than the median) which is clearly reflected also in the statistics and the graphs. The highest average number of patients who have the Influenza virus is in Mecklenburg-Vorpommern (59.61). The lower number of patients who have the virus is in the Land of Hamburg (0.40), while the highest is reported for the state of Saxony (307.20).

This dataset incorporates patients from 16 federal states (as they are incorporated in the RKI reporting system) in Germany and covers a chronological span of 16 consecutive years. To determine potential differences between mean patient numbers among different states, a statistical approach was followed. We proceeded by checking for equality employing the tests ANOVA and KRUSKAL-WALLIS. The hypothesis of equality of means was rejected, so the corresponding state plays an important role statistically.

Table 6: ONE WAY ANOVA cases by (State).

Analysis of Variance Table

Response: Cases

	DF	Sum of Square	MS	F value	$Pr(>F)$
State	**15**	**111326**	**7421.7**	**2.3753**	**0.003298**
Residuals	**239**	**746752**	**3124.5**		

Table 7: ONE WAY ANOVA cases by (Year).

Analysis of Variance Table

Response: Cases

	DF	Sum of Square	MS	F value	$Pr(>F)$
Year	**15**	**475370**	**31691**	**19.791**	**<0.001**
Residuals	**239**	**382708**	**1601**		

Table 8: TWO WAY ANOVA cases by (State) and (Year).

Analysis of Variance Table

Response: Cases

	DF	Sum of Square	MS	F value	$Pr(>F)$
State	**15**	**111326**	**7422**	**6.1635**	**<0.001**
Year	**15**	**477024**	**31802**	**26.4101**	**<0.001**
Residuals	**224**	**269728**	**1204**		

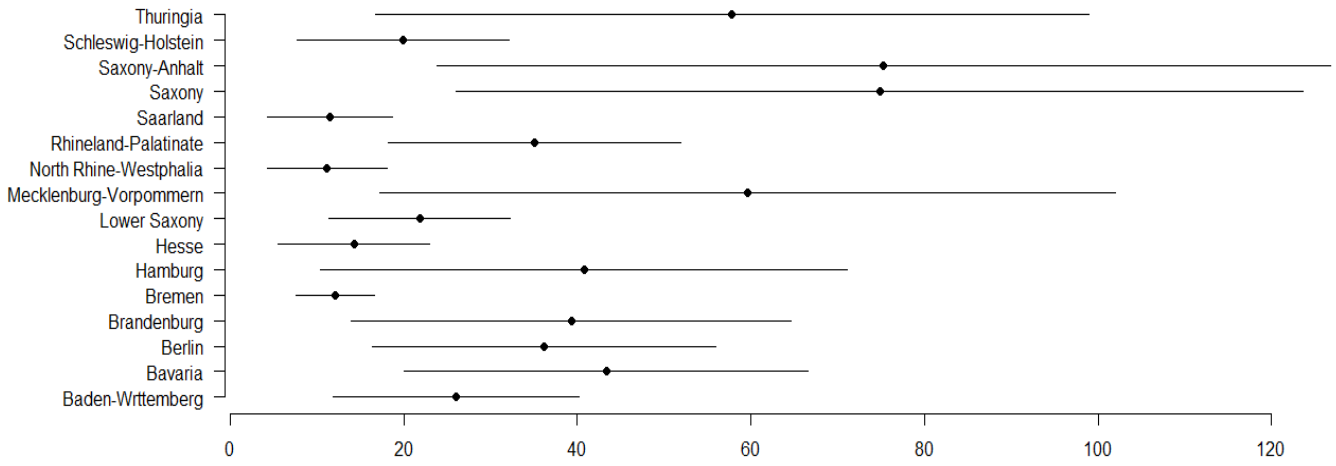


Figure 3: Error bar cases by (State)

The analysis in **Table 6** reveals that the State is statistically significant. There is no difference in the number of cases per state, therefore the average number of cases is different per state. This is also clearly illustrated from **Fig 2** that covers all represented states and influenza cases within these states with means and error bars. Is in fact visible that the confidence intervals of the cases depicted on the federal states as well as we are able to notice that some of those have no common points, thus rejected the equality of means.

Table 7 depicts that the Year is statistically significant, as there is no difference in the number of cases per year. The average number of cases is different every year, and this is clearly observed in **Fig 3** (error bar / means diagram) where there is a (total) growth trend of average number of cases over time.

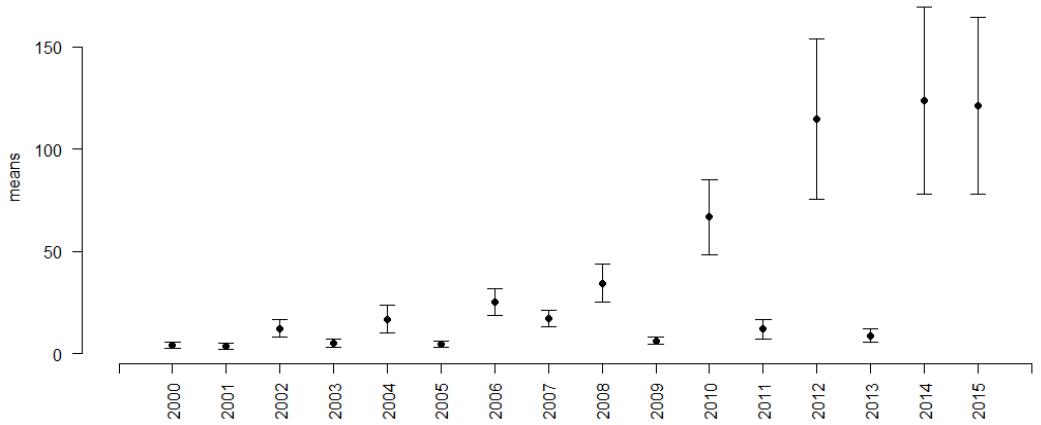


Figure 4: Error bar cases by (Year)

The mean error-bar plots reveal additional differences for age groups (**Fig 2S A, B**) as well as individual states (**Fig 3S A, B)**. **Fig 2S** emphasizes in two age groups (0-4, A and 5-14 B) where years with no cases are reported, years with no statistical significance are also visible with the majority of occasions to share statistical significance. **Fig 3S** and the two indicative example-states Bavaria (A) and Berlin (B) provide a similar picture pinpointing the need for a secondary deeper analysis of the data-set available.

Table 8 dictates that while the State and Year is statistically significant, there is a difference in the number of cases per year, and also per state.

What become evident in the Kruskal-Wallis test ($P < 0.015$) and in the head to head comparison of the separate states with the Dunn's Multiple Comparison Test (**Table S2**). According to this statistical significant differences can be verified only for the pairs North Rhine-Westphalia vs Saxony ($P<0.05$) and North Rhine-Westphalia vs Saxony-Anhalt ($P<0.05$) respectively. This analysis clarifies that the differences observed for the different federal states in their majority are not statistically significant in the Kruskal-Wallis test.

This doesn't underestimate the substantial differences observed between states. These differences can be visualized in a frequency distribution histogram where the % of frequency of occurrence per state is represented (**Fig 4**)

We retrieved the same database (SurvStat@RKI2.0) and assembled the same patient dataset that includes cases per 100,000 inhabitants per time period from the federal German states, in the time period (2000-2015) but we incorporated a filter for distinct different age groups. These age groups are from 0 – 4, 5 – 14, 15 – 44, 45 – 64 and >65 years old respectively.

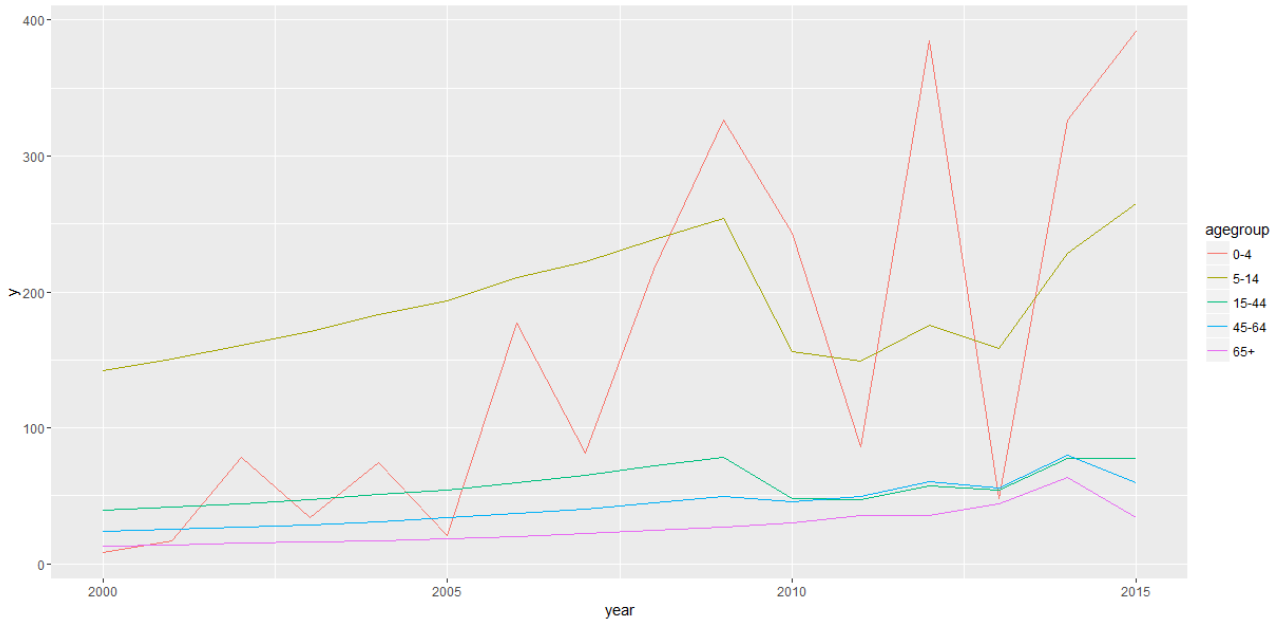


Figure 5 : Line plot about rates in time by age groups

Fig 5 Illustrates rates of cases per age group through time (2000-2015) where is evident that the younger brakets (0-4, 5-14) are more susceptible to influenza. This pattern is directly related with time. The 0-4 age bracket, has a quite variable response in the first 5 years of the time frame examined (2000-2005) and although remains variable within the next 10 years (2005-2015) appear significant spikes in observed rates. These spikes are potential ourbreaks and appeared reletively consistent occured in three year time periods (2006, 2009,2012,2015) respectively. The pattern may be more complicated but it requires additional information for a more coherent examination. The 5-14 age bracket appears more consistnt with higher rates of influenza infected patients between the years 2000-2009. This rate is increasing lineary through time and around 2009 exhibits a drow couples with relative pattern inconsistency. Despite the observed high rates (at least higher than all the other age groups but the 0-4) the 0-4 group outbreaks exhibits higher rates.

There are also hints that the 0-4 and 5-14 brackets patterns share some similarity during the 2009-2015 time frame, as for example for every 0-4 spike there is a less pronaunce 5-14 spike, but this analysis will require more information in order to be thoroughly explained. The brackets corresponding to older ages are far more consistant with limited variation through time and presenting a limited number of influenza infected patients. It is also worth noticing, that this analysis, illustrate less number of patients as the age is increasing. Generally, influenza patients are closer to 50 for each category (15 – 44, 45 – 64 and >65) with the 15-44 group to clearly reaching over 50 cases through time and for the longest period of time (2005-2015 with the possible exception of year 2011). The age group 15-44 reaches and surpass 50 cases in years 2012-2015 with this increase to be marginal and relatively less significant when compared with the 15-44 group. The oldest portion of the population has a negligible spike in 2014 where marginally the cases are reaching beyond 50. The pattern comparison is extremely interesting and may also provide additional information regarding the immune response of the patient as well as the total response in combination of course with additional not necessarily statistic information.

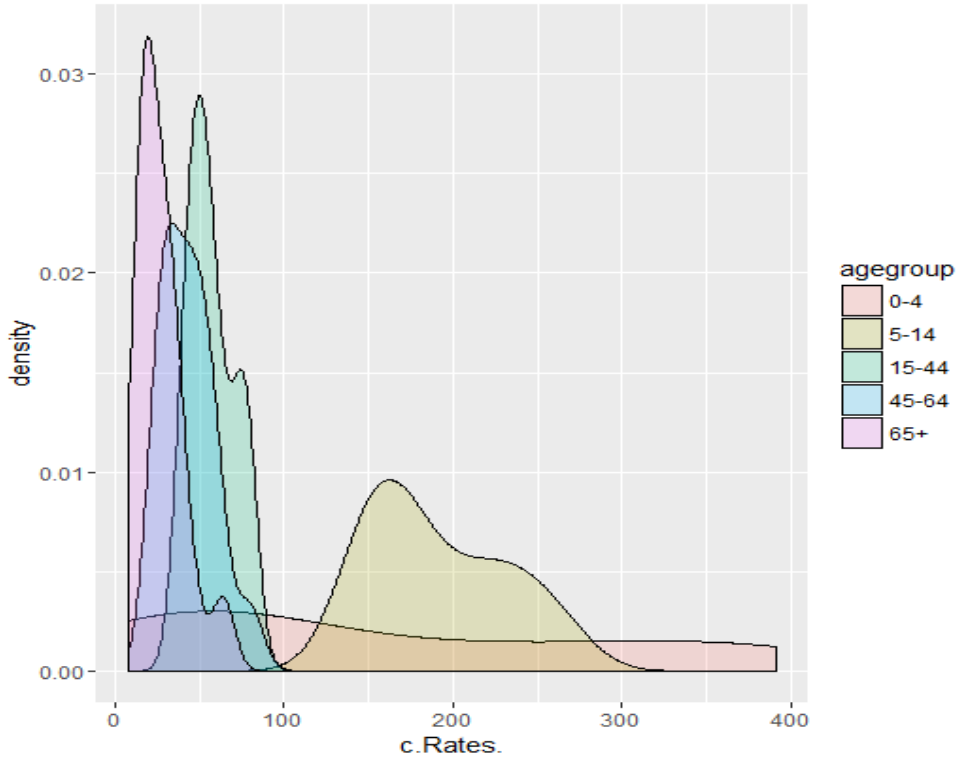


Figure 6 Histogram that correlates density of events with influenza infection rates for the selected age groups in patients from the German federal states reporting system

Fig 6 provides more insight for the pattern of influenza infectious diseases rates in German federal states It is worth noticing, that the most dense are the one corresponding to the oldest age brackets (15 – 44, 45 – 64 and >65) but the infection rates are extremely. As it is illustrated in Fig in all these cases we are discussing for less than 100 incidences. On the contrary the influenza cases stemming from the younger segments of the population (0-4, 5-14) are not as dense (dense rarely goes above 0.01) but the rates of cases appear consistently high. In other words, the high level of cases in the latter occasion are not consistent and frequent but leads to higher numbers of infected individuals. This analysis correlates well with the previous **Fig 5** and in fact it complements it. The inconsistency observed before is illustrated with accuracy in this one. Another very important item, has to do with the distinct differentiation between age group 0-4 and 5-14 rates. Age group 0-4 presents a huge variation of rates (0-400) and 5-14 although variable (100-300 plus) is in between the younger and the oldest age brackets in terms of variability. This late observation of course correlates well with all the illustrations in **Fig 3.**

The analysis in **Table 9,10,11** reveals that the age Group is statistically significant. The average number of cases is different per age group. This is also clearly illustrated from **Figures 5** and **6** that covers all represented states and influenza cases within these age groups. Is in fact visible that the confidence intervals of the cases depicted on the age groups as well as we are able to notice that some of those have no common points, thus rejected the equality of means.

This was evident in the Kruskal-Wallis test ($P< 0.0001$) and in the head to head comparison of the separate age groups with the Dunn's Multiple Comparison Test (**Table S1**). According to this statistical significance can be verified for 0-4 *vs.* >65 ($P< 0.0001$), 5-14 *vs.* 15 – 44 ($P< 0.05$), 5-14 *vs.* 45-64($P< 0.0001$), 5-14 *vs.* >65 ($P< 0.0001$), 15 – 44 *vs.* >65 ($P<0.05$) respectively. This analysis clarifies that the differences observed for the older population group are statistically significant against all other population groups throughout the time frame evaluated in this study, followed by the 5-14 group that exhibited significance against all but the 0-4 group, the 15-44 group where as in the case of the 0-4 group significance was sporadic and was exhibited only against the older group.

Table 9 ONE WAY ANOVA cases by (Age Group).

Analysis of Variance Table

Response: rates

	DF	Sum of Square	MS	F value	$Pr(>F)$
Age Group	**5**	**349900**	**87470**	**20.52**	**< 0.0001**
Residuals	**75**	**319700**	**4263**		

Table 10 ONE WAY ANOVA cases by (Year).

Analysis of Variance Table

Response: Cases

	DF	Sum of Square	MS	F value	$Pr(>F)$
Year	**16**	**117700**	**7847**	**0.9100**	**0.0184**
Residuals	**79**	**551900**	**8623**		

Table 11 TWO WAY ANOVA cases by (Age Group) and (Year)

Analysis of Variance Table

Response: Cases

	DF	Sum of Square	MS	F value	$Pr(>F)$
Age Group	**4**	**349900**	**87470**	**25.98**	**<0.001**
Year	**15**	**117700**	**7847**	**2.331**	**0.0107**
Residuals	**60**	**202000**	**3366**		

The assessments and the observations that are reflected from the cumulative data, statistics and graphical representation when dissected in separate analysis for each federal states reveal some interesting patterns critical for the overall influenza surveillance in Germany for the years 2000-2015. There are obviously some common features worth noticing.

There are 3 different period-patterns based on the frequency influenza of incidences, 2000-2005, 2005-2009, 2009-2015. The number of cases is gradually increasing, starting off from extremely low numbers (2000), following by moderately but worth mentioning low numbers (2009) and reaching a significant number of infected patients at the end of this period (2005) with a substantial spike in 2014.

This pattern applies for the majority of federal states excluding in principle Bremen where the pattern is inconsistent through time (**Fig S1, E**). Unlike all the other federal states, in Bremen the number of spikes appears in a few years (2002, 2010, 2012) and the number of cases corresponding to 2014 is extremely low. Another case of relative inconsistency appears in the case of Lower-Saxony (**Fig S1, I**) but the general pattern is closer to the other states.

The 3 patterns share also some additional features that in a degree may be expected: The first time period as a lower degree of variability with the pattern inconsistency to

appear enhanced but close to the first in the second. Notable exception to this pattern is the increased variability observed in Bremen, Lower-Saxony and Mecklenburg-Vorpommern (**Fig S1, E, I, H**). The third time period has higher, noticeable number of cases, that are not consistent and may very well be attributed to potential influenza outbreaks. There is not a German federal state with a regular, consistent per year pattern. Apart from the repetitive pattern of high influenza frequency in all, there is a constant repetition from a year where the number of cases is diminished. The only exception to this observation, lies in the last two years of this time frame (2014, 2015) where the results in terms of infected patients are comparable and stay relatively high. There is also a variation among federal states, for the pattern that relates both frequencies in 2014 and 2015. In a number of cases there is an incline observed and in a significant number of federal cases a minor decline. These alterations will be probably more challenging to interpret but safe assumptions can be made.

5.2 Model-based inference

acp model

```
acp.formula(formula = value2/10 ~ as.factor(AgeGroup) + as.factor(State) +
    trend + cos12 + sin12, data = Data, p = 2, q = 0)

                                      Estimate     StdErr  t.value   p.value
(Intercept)                         -4.1259265         NA       NA        NA
as.factor(AgeGroup)05.14            -0.0032165  0.0205350  -0.1566 0.8755338
as.factor(AgeGroup)15-44            -0.0194871  0.0259370  -0.7513 0.4524599
as.factor(AgeGroup)45-64            -0.0198165  0.0282564  -0.7013 0.4831111
as.factor(AgeGroup)65+              -0.0233307  0.0307362  -0.7591 0.4478191
as.factor(State)Bavaria              0.3854640  0.0483886   7.9660 1.664e-15 ***
as.factor(State)Berlin               0.2913179  0.0485850   5.9960 2.032e-09 ***
as.factor(State)Brandenburg          0.4159457  0.0476232   8.7341 < 2.2e-16 ***
as.factor(State)Bremen              -0.0879905  0.0535172  -1.6442 0.1001486
as.factor(State)Hamburg              0.4519958  0.0486144   9.2976 < 2.2e-16 ***
as.factor(State)Hesse               -0.0135208  0.0529510  -0.2553 0.7984567
as.factor(State)Lower Saxony         0.1709144  0.0501580   3.4075 0.0006559 ***
as.factor(State)Mecklenburg-Vorpommern  0.7519567  0.0462483  16.2591 < 2.2e-16 ***
as.factor(State)North Rhine-Westphalia -0.0586292  0.0542775  -1.0802 0.2800676
as.factor(State)Rhineland-Palatinate  0.4627064  0.0491506   9.4141 < 2.2e-16 ***
as.factor(State)Saarland            -0.0298817  0.0541508  -0.5518 0.5810704
as.factor(State)Saxony               0.9433276  0.0454368  20.7613 < 2.2e-16 ***
as.factor(State)Saxony-Anhalt        1.0089142  0.0431439  23.3848 < 2.2e-16 ***
as.factor(State)Schleswig-Holstein  -0.0650253  0.0520272  -1.2498 0.2113646
as.factor(State)Thuringia            0.7509914  0.0455228  16.4971 < 2.2e-16 ***
trend                                0.0300209  0.0326909   0.9183 0.3584517
cos12                               -0.0040611  0.0112383  -0.3614 0.7178313
sin12                                0.0303160  0.0110485   2.7439 0.0060732 **
a                                    0.0102011  0.0082359   1.2386 0.2154897
b 1                                  6.6076569         NA       NA        NA
c 0                                 -1.2676164         NA       NA        NA
c 1                                  0.8698458  0.0054858 158.5628 < 2.2e-16 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Logl:
[1] -27035.25

AIC:
[1] 0.7977963

BIC:
[1] 0.8012934
```

We retrieved the same database (SurvStat@RKI2.0) and assembled the same patient dataset that includes cases per 100,000 inhabitants per time period from the federal German states, in the time period (2001-2016), with the same filter for distinct different age groups. These age groups are from 0 – 4, 5 – 14, 15 – 44, 45 – 64 and >65 years old respectively.

zip model

```
zeroinfl(formula = floor(value/10) ~ State + AgeGroup + Year + Period | Period,
    data = Data[-I, ])

Pearson residuals:
      Min        1Q    Median        3Q       Max
 -0.43205  -0.18799  -0.06831  -0.02923 197.78862

Count model coefficients (poisson with log link):
                            Estimate Std. Error z value Pr(>|z|)
(Intercept)                -1.056574   0.122740  -8.608  < 2e-16 ***
StateBavaria                0.758822   0.119279   6.362 1.99e-10 ***
StateBerlin                 0.564986   0.121632   4.645 3.40e-06 ***
StateBrandenburg            0.851158   0.116380   7.314 2.60e-13 ***
StateHamburg                0.980258   0.117401   8.350  < 2e-16 ***
StateLower Saxony           0.344346   0.130229   2.644  0.00819 **
StateMecklenburg-Vorpommern 1.273477   0.111718  11.399  < 2e-16 ***
StateRhineland-Palatinate   0.866543   0.119812   7.233 4.74e-13 ***
StateSaxony                 1.364407   0.110565  12.340  < 2e-16 ***
StateSaxony-Anhalt          1.557804   0.109022  14.289  < 2e-16 ***
StateThuringia              1.418499   0.110679  12.816  < 2e-16 ***
AgeGroup05.14               0.098020   0.031682   3.094  0.00198 **
AgeGroup15-44              -1.608343   0.063397 -25.369  < 2e-16 ***
AgeGroup45-64              -2.441922   0.088101 -27.717  < 2e-16 ***
AgeGroup65+                -3.412213   0.134624 -25.346  < 2e-16 ***
Year                        0.102463   0.004632  22.120  < 2e-16 ***
PeriodHot_Period           -1.036712   0.115964  -8.940  < 2e-16 ***

Zero-inflation model coefficients (binomial with logit link):
                Estimate Std. Error z value Pr(>|z|)
(Intercept)      1.55703    0.03287   47.37   <2e-16 ***
PeriodHot_Period 3.05594    0.14513   21.06   <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Number of iterations in BFGS optimization: 30
Log-likelihood: -1.007e+04 on 19 Df
```

The results from both models indicate relative convergence for the zip model, but not for the acp model when this include the non-statistical significant values. Nevertheless it is visible a trend that correlates frequency of cases and Age Group. The number of estimated cases appears to decrease as the age bracket is increasing leading to a minimum estimation for the 65+ group (-0.0233 for the acp and -3.412 respectively) . Despite the statistical variation that is visible for both models, there is an additional trend occurring for the estimate of cases per state as it is reflected from the observation that states with the higher estimate are aligning in both models.

Most notable are the estimates for Saxony-Anhalt (1.55 and 3.39 and Thuringia (1.41 and 2.78 respectively). The same trend seems to apply in states where case estimates is the lowest (for example Lower Saxony).

This dual clarification reflects a trend for the state and age group estimation and allows further analysis.

Table 12. Summary of Poisson and binomial analysis

		95% Confidence interval	
	$e^{\hat{b}}$	2.5 %	97.5 %
Poisson part (P(Y>0))			
Intercept	2,7529	2,6344	2,8767
Bavaria	1,5670	1,4971	1,6401
Berlin	1,4409	1,3750	1,5100
Brandenburg	1,8948	1,8111	1,9823
Bremen	0,9275	0,8739	0,9845
Hamburg	1,8725	1,7894	1,9595
Lower Saxony	1,2363	1,1758	1,3000
Mecklenburg-Vorpommern	2,8225	2,7045	2,9456
North Rhine-Westphalia	0,8232	0,7734	0,8763
Rhineland-Palatinate	1,6678	1,5926	1,7466
Saarland	0,8774	0,8249	0,9332
Saxony	2,8381	2,7217	2,9594
Saxony-Anhalt	3,3926	3,2568	3,5342
Thuringia	2,7897	2,6747	2,9096
5-14	1,4150	1,3930	1,4374
15-44	0,4621	0,4508	0,4737
45-64	0,2981	0,2884	0,3080
65+	0,1678	0,1592	0,1768
Year	1,0908	1,0888	1,0927
Period_Summer	0,2718	0,2624	0,2816
Binomial part (P(Y=0))			
Intercept	2,6854	2,6083	2,7649
Period_Summer	8,6746	8,0569	9,3396

Poisson analysis. By removing the non statistical significant federal states of Hesse and Schleswig-Holstein) and applying as a level of reference the state Baden-Wurttemberg and the age group of 0-4 years there are the following observations:

- There is an increase in the estimated cases around 9%. for every increase in the Year increments
- There is a substantial, quantifiable decrease for the estimated cases number of 73% [(1-0.27)*100] during the summer period when compared with the winter months given that every other variable under consideration by the model remains constant

- The estimated cases in Brandenburg is at 89% higher when compared with the reference level (state of Baden-Wurttemberg) given that every other variable under consideration by the model remains constant
- The estimated cases in the aged bracket 65+ is calculated at 83% [(1-0.17)*100] lower when compared with the reference level age group 0-4) given that every other variable under consideration by the model remains constant

Binomial analysis The binomail analysis provides an estimate for the seasonal impact of flue as the prediction was that cases during the summer months are approximately 8.67 less possible when it compared with the winter months (pattern that fits to already existing patterns and existing flu predictive models, see *discussion* for detail) .

6. Discussion

The Federal Republic of Germany has a long standing tradition of increased influenza case numbers throughout the individual states. This fact is reflected with a number of deaths throughout the pandemics as well as the epidemic seasons. There is a clear variation between the federal states as it is reflected from (Die, 2017) where the flu hits harder in some when compared with others. This is reflected simply with number of cases and not with additional statistical analysis.

In the last influenza season in Germany, from October 2016 till the first week of February 2017 the total toll of deaths have been above 100 and the confirmed influenza cases reached 43000. The first week up to February 5th saw more than 14000 confirmed cases in all federal states that includes 32 larger outbreaks reported. According to Silke Buda from the RKI "A lot of people are complaining of respiratory problems that are generally caused by influenza." The epidemics has already reached a death toll of 126, that are mainly senior citizens over the age of 60.
The infection outbreaks are attributed to the H3N3 type of virus, that has been also a dominant killer in Germany in the winter of 2014-15. Dr. Buda suggested caution, as the virus can cause unimaginable damage when large crowds are gathering in the schooling system as well as in the healthcare and retirement facilities. The federal states suffered most from the outbreak were Bavaria and Baden-Württemberg with 6,275 confirmed infections between January 30th and February 5th. The problem appeared equally severe in Eastern Germany, including Berlin where 5,455 new cases have been reported. The toll was less severe in the west where 2,529 new cases from Saarland up to North Rhine-Westphalia have been reported. The threats of large crowds and gatherings remained and RKI and the public health officials push forward towards the avoidance of events that may made the situation more complicated. The only regions that experienced a less severe version of the epidemic was the northwest part of Germany where only 1,115 new cases were reported in the first week of February
According to what it has been observed the seasonal influenza epidemics regularly lead to a gradual increase in the mortality rates in Germany (Huy, 2012). The trend is quite similar in other western European industrialized nations as well as globally. In a relatively recent study, there is a more specific and statistically important study that

follows all these mortality rates and the seasonal influenza wave variation. The federal state of Baden-Wuerttemberg was selected and a number of cases and relevant data were retrieved. The time frame that has been selected was 2001-2006 and an attempt to implicate the role of the environmental temperature was made. This within the frame of visual methodology and statistics. The mortality peaks were correlating with viral influence waves and notably, they were coming after exactly an environmental temperature drop. The numbers of death causality during epidemics they correlate with chronic co-existing conditions, the environmental temperature factor and a variety underlying diseases in different level of escalation when the seasonal epidemic arrived. The general conclusion was that the number of deaths and the overall impact of viral influenza mortality was severely underestimated in Baden-Wuerttemberg and by extrapolation in Germany

.

The Influenza pandemics have been associated with an extensive number of deaths and prolonged illnesses and hospitalizations. Each pandemic differs, from the way of manifestation where a gray uncertain area always exist, to the way that the virus emerges, expand, getting diagnosed and potentially treated (Lehners, 2013). A classic recent and relative to this work example is the novel influenza A (H1N1) pdm09 virus that emerged in Mexico in April 2009 and instantly spread out globally (Fraser, 2009). It is worth mentioning that the nature of an influenza infection is generally self-limiting with systemic and respiratory symptoms that often resolve in less than one week. Most people infected with the 2009 A (H1N1) pdm09 virus experienced uncomplicated illness and recovered fully within one week, even without any therapeutic intervention; only one small subset of patients developed progressive disease (Cullen, 2009). In principle viral pneumonia was the most common from the findings in severe cases, but secondary bacterial infections played a pivotal role in approximately 30% of fatal cases ((CDC), 2009). Patients that spent time in the hospital, were often affected by co-morbidities, with a list that includes diabetes, cardiovascular, neurological and pulmonary diseases (Jain, 2009b). The therapeutic advances in cancers, autoimmune diseases, late-stage of organ failure related diseases prolonged survival, but this increased physiological challenge lead to an increased number of immunosuppressed patients. This, leads to a vicious cycle increasing the risk for patients to acquire opportunistic and community-acquired infections, such as

respiratory virus infections, increasing considerably the number of illnesses and deaths (Ljungman, 1993).

Although patients hospitalized during the pandemic with the viral A(H1N1)pdm09 infection got a subsequent severe illness, the overall number of people died was initially overestimated. The overall mortality rate from this pandemic was similar to that attributed to seasonal influenza and for sure lower than that of previous enumerated pandemics (Donaldson, 2009). Most victims died by respiratory failure (Estenssoro, 2010). Other reported causes of death included pneumonia, high fever (it lead mainly to neurologic sequelae), dehydration (from excessive vomiting and diarrhea), as well as electrolyte imbalance. The eldest patients, were related more frequently with severe cases as a result of chronic and co-existing conditions (Estenssoro, 2010). The virulence pattern between A(H1N1)pdm09 strains and seasonal influenza strains appear to be similar, the course of the pandemic attributed virus seems to get a more aggressive course in specific populations, that include young patients and pregnant women (Chowell, 2009; Jamieson, 2009). Further risk factors include obesity, chronic manifested conditions (lung disease, heart disease, renal disease, diabetes mellitus), and severe immunosuppression (Jain, 2009a; Influenza, 2010). The results reported with respect to the infection severity during the pandemic season are also conflicting. A number of researchers supported that there are no differences in terms of the disease severity among the first and the second pandemic outbreaks in 2009 (Ramakrishna, 2011). In retrospective there is a study available that reports a 4-fold increase in hospitalized patients and a 5-fold increase in the mortality frequency in the second pandemic wave (Truelove, 2011). The fact remains that the data available regarding mortality and disease frequencies among the first and second waves in 2009 remain purely analyzed and elusive.

A retrospective analysis was performed of all patients with laboratory-confirmed influenza A(H1N1)pdm09 virus infection who were hospitalized at the University Hospital Heidelberg, Germany, in the pandemic season 2009–10 and the first post pandemic season 2010–11 to compare the rates of severely diseased patients in both seasons and to identify possible risk factors associated with severe clinical outcome.

An factor analysis for the severity of the clinical outcome in patients taht have been treated in the hospital with influenza A(H1N1) pdm09 infection with laboratory-confirmed findings in years 2009, 2010 (pandemic and first post-pandemic seasons)

within the University Hospital Heidelberg system. 102 patients identified in 2009–10 and 76 in 2010–11. The severity for hospitalized patients was increased dramatically from 14% (2009–10) to 46% (2010–11) and the same applies for the mortality rate (5%–12% respectively). The patients in the that first post pandemic season belonged to an older age group (38 vs. 18 years) and the infection was coupled with co-existing medical conditions (75% vs. 51%). 28% of these patients had a severe clinical outcome, resulting in 14 deaths. The general trend and the overall analysis, revealed enhanced fatal cases in the post pandemic season. This fact basically, reinforces the argument that early medical care hospitalization and treatment will be the only way to reduce mortality in the future.

The data available for the circulation and transmissibility of the avian influenza in Latin America provide also a picture that is scary not only in poultry and wild birds. A systematic review identifies that the characteristics of the AIVs can generate new viral variants that can elevate events beyond the outbreak to the zoonotic and pandemic potential (Afanador-Villamizar, 2017) There is a lack of understanding for the effect of these viruses in a regional level, especially in Latin America where they have been extensively identified. A systematic analysis based on the PRISMA and STROME guidelines peer reviewed research published between 2000 to 2015 and classified based on country, viral subtype, avian species, and phylogenetic origins. 271 studies were initially detected, but only twenty-six met the inclusion criteria. The AIVs-driven infections were detected in all Latin American countries with a ranking between the predominant Mexican research for the period that the study was performed towards Chile and Argentina that followed the list. The majority of the AIVs subtypes suvvelied and reported were of low pathogenicity and virulence (92.9%) and a small fraction was of high pathogenicity (7.1%). Apart from the specific details from the origin of the AIVs (whether they carry a domestic bird origin, the order that they belong etc). It was clear that the field was not exploied extensively as even the map of the AIVs in South America is far from completed.

Avian influenza viruses such as the A(H5N8) are highly pathogenic and they have correlated since 2010 with extensive outbreaks mainly in the region of the south-east Asia. The A(H5N8) virus was first detected in domestic ducks in China during routine surveillance activities at a live poultry market (Wu, 2014). Since the beginning of 2014, several outbreaks involving novel reassortant influenza A(H5N8) viruses have

been detected in poultry and wild bird species in South Korea (Jeong, 2014) as well as in China (Wu, 2014; Fan, 2014). The viruses have been detected in captured and apparently healthy wild migratory birds and dead wild birds, as well as in domestic chickens, geese and ducks (Jeong, 2014; Fan, 2014). Avian influenza A(H5N8) viruses have shown moderate pathogenicity in domestic ducks in South Korea (0–20% mortality rate) and do not cause severe illness or death in wild mallard ducks. One study reported that viral replication and shedding was greater in mallards infected with A(H5N8) influenza viruses than in mallards infected with A(H5N1) viruses. Transmission of A(H5N8) viruses between wild bird species and poultry/domestic birds may occur by direct contact. Mammals such as ferrets, dogs and cats can be infected experimentally, but results indicate that a recent H5N8 isolate was less virulent in mice and ferrets than (A)H5N1 in mammalian species (Kim, 2014). Natural infection of dogs with A(H5N8) has been reported from South Korea. Avian influenza A(H5N8) viruses from South Korea bind strongly to alpha 2-3 sialic receptors and, to a lesser degree, to alpha 2-6 receptors (Kim, 2014). However, the results from the ferret model are inconclusive in terms of virulence for humans. The spread of the virus may occur via migratory bird flyways (Fan, 2014; Kang, 2015). Legal import of live poultry and live captive birds into the EU is not authorized from the east Asian region. Treated egg products and eggs for processing may be imported into the EU from South Korea and China. Heat-treated poultry meat products are authorized for import into the EU from South Korea and from one Chinese province (Shandong). No imports of any poultry commodities are permitted from Japan, where outbreaks caused by the H5N8 virus have also occurred. Given the very heat-labile nature of all influenza viruses, these commodities are not considered to pose a risk of influenza virus transmission to consumers. No human cases of avian influenza A(H5N8) have been reported related to the current circulating virus. Event background information Germany notified the European Commission and the World Organization for Animal Health (OIE) on 6 November 2014 of an outbreak of highly pathogenic avian influenza of subtype H5N8 at a poultry holding in the north-east of Germany (OIE, 2014). The holding was keeping approximately 31 000 fattening turkeys, 5 000 of which were infected, and 1 880 died within two days. The outbreak affected 15-week-old birds in one of five sheds at the holding. An increase in mortality was observed after 1 November 2014 and a private laboratory subsequently identified an avian influenza A(H5) virus. The National Reference Laboratory for

avian influenza at the Friedrich-Loeffler-Institute (FLI) in Germany confirmed the highly pathogenic avian influenza A(H5N8) on 5 November 2014. The virus is of South Korean origin, clustering in clade 2.3.4.6. There was no evidence of this virus being present in wild birds captured for routine surveillance. The reference laboratory reported that the virus is detectable using EU-recommended laboratory methods (M 1.2 and H5). The authorities placed the infected holding under restrictions as of 4 November 2014 and took measures required by Directive 2005/94/EC, including the establishment of a protection zone of 3 km radius and a surveillance zone of 10 km radius (Commission, 2014). Culling and safe disposal of the turkeys at the infected holding started on 6 November 2014 and poultry kept at other farms located within the protection zone were also culled. These actions were completed by 8 November 2014. Investigations have been initiated at poultry holdings within the surveillance zone to try to determine how the virus entered the turkey holding. Germany reported that no live poultry or poultry meat from the affected holding has been shipped to other regions of Germany, other EU Member States or third countries.

On 6 November 2014, the German authorities have reported an outbreak of the highly pathogenic avian influenza virus A(H5N8) at a turkey holding facility. When the H5N8 was initiated the response of developing and establishing protection and surveillance zones was instant aiming in identifying the causative effect. A(H5N8) has been detected among wild birds in southeast Asia and has been the causative agent for many outbreaks on farms that carry poultry in S. Korea and China. The 2014 outbreak is the first relative outbreak in Europe and up today it remains perplexing the appearance of the virus in the German turkey holding. The level of such a public health threat has been assessed and found to be in a minimal level. The reported datasets globally leading to the same conclusion as no human infections have been reported as well as the EU/EEA monitoring systems predict that the risk of zoonotic transmission is considered insignificant and below reportable levels.

Nevertheless, the capabilities of this extremely virulent avian influenza virus to infect wild birds with the absence of typical symptoms, increases the threat of extensive geographical spread, that may lead to outbreaks like the ones observed in South Korea. The systems of robust monitoring and virulence assessment for wild birds as well as domestic poultry remains important in EU and tightly connected with the detection of other virus occurrences. The viable threat of viral spread prompt the EC

to issue the Directive 2005/94/EC that requires Member States to have prepared and execute contingency plans and detailing defined measures for the eradication and secure disposal of infected poultry, all the potentially contaminated equipment as well as the procedures and methods for cleaning and disinfection. Every person in direct contact that handles diseased poultry, turkey or other birds (this list includes farmers, veterinary and labor personnel), are by definition at risk. Public health authorities should work in collaboration to enforce contingency plans to protect everyone exposed and foresee which one on site or on proximity is in viable danger to be potentially protected from infection.

The hypothesis that the avian influenza may infect human as well as transferring in other organisms was formulated in the hype of the H5N1 strains occurrence in Asia (Lewis, 2006). The hypothesis was based on the fact that H5N1 was in fact infecting humans causing outbreaks and deaths. This become evident in other mammals such as cats and pigs. This evidence was crucial to suggest that the possibility of a pandemic exists, as a human to human transfer will prompt the occurrence of additional mutations, as well as the possibility of additional mutations in the human IVAs, will make them resistant in the current antiviral and vaccines available.

The threat of avian influenza spread in migratory birds and poultry has been urging the affiliated with influenza surveillance but also other relative professionals to closely monitor and evaluate these trends (Riley, 2007). Do these trends share the possibility to upgrade in a precursor of a human pandemic like the previous ones and specifically the 1918-like one? The supply and available stockpiles of human pre-pandemic vaccine, that targets the avian strains are being considered as a formidable alternative. There are obvious constrains and limitations to deploy these stockpiles with the major one being the total amount of the antigen can be contained. For a number of countries around the word, these constrains form a real hesitation with respect to the total amount of antigen contained in the vaccine. For many countries, the principal constraint for these vaccine stockpiles will be the total mass of antigen maintained. A hypothesis that even these lower dosage which lies below the recommended therapeutic dosage for complete protection maybe a sufficient preventive tool as the wider vaccine coverage and usage of the vaccine stockpile has a benefit and not generating a problem.

To test this hypothesis, mathematical models that have validity taking under consideration different datasets and policies have been developed. For example, a

prominent one, incorporates the individual response to different doses of a potential vaccine but also includes the process of individual transmit ion of the pandemic influenza from a person to another. It was demonstrated that the reduction in the infection attack rate are significant especially when vaccines are up taken by more people in lower dosage. The data applies equally for the 3 vaccine candidates available. The major attempt here is to understand the magnitude of the effect and this has been achieved by epidemic simulation deploying the available historical studies on immunogenicity. As an example of the approach it should be highlighted that for one out of the three vaccines with available data, the infection attack rate would drop 9.9% (from 67.6% to 58.7%) if an optimal vaccine dose is given in approximately 50% of the US population. In retrospective, when the maximal protective dose (as it is determined from the US National Pandemic Preparedness Plan) the attack protected general population would be significantly lower than 10%. These data don't reflect in accuracy the number of alternative events and possibilities that will define in detail the nature of the vaccine protection. This is a model one way or another. The different population groups including the sensitive where the infection rates are always higher (infants, elderly) has not been assessed. A number of other similar factors have been under evaluated.

In conclusion, it appears as totally necessary to take under consideration the population-based implications for the designed vaccine programs. These considerations are directly related with dose and stockpile size. Reducing th vaccine dosage will not harm, in fact it may be more productive as more people will be covered and maybe some of the potential adverse effects will minimize.

Surveillance

The IAVs can be transmitted in humans via aerosol and intercontinental spread that is facilities by migratory birds. This complex situation complicates on the one hand surveillance, but on the other hand this is the most critical point to manage globally IAVs (Donatelli, 2016; Alexander, 2000). WHO has established a Global Influenza Surveillance and Response System (GISRS) consisting from a number of collaborating centers and reference laboratories. The GISRS has 113 member states that contribute by conducting influenza virus surveillance and update on a regular basis for recommendations that define the laboratory diagnosis, the use of the most

appropriate vaccines, the existing and projecting antiviral susceptibility tests as well as the overall risk assessment. Most importantly, GISRS provides global alerts on the emergence of novel influenza viruses including of course potential outbreaks and pandemics.. This task list makes GISRS a single point, timely reference source on worldwide status and management of the influenza virus, including drug-resistant phenomena that complicate even more IAV-mediated infections. GISRS works closely with CDC which also have a tendency to act as a consistent reporter for updates and advisories on IVAs.

There are indeed data that support the increased presence of incidences in the pediatric intensive care units (PICU) following the 2009 pandemic (Streng 2015). This has been evaluated with active screening of the clinical characteristics and the incidence for children during the first three post-pandemic influenza seasons. According to this evaluation, a total of 24/7/20 influenza-associated PICU admissions were noticed in the respective post-pandemic seasons 1/2/3;. The incidence estimates per 100,000 children were 1.72/0.76/1.80, respectively. Out of the total 51 patients, 80% was infected with influenza A, including 65% with A(H1N1)pdm09. The pandemic causative agent H1N1 pdm09 was virtually absent in season 2 (incidence 0.11), but was dominant in PICU admissions for seasons 1 (incidence 1.35) and 3 (incidence 1.17). According to the available clinical data for 47 influenza patients; the median age was 4.8 years (IQR 1.6-11.0). The most frequent diagnoses varied from influenza-associated pneumonia (62%), followed by bronchitis/bronchiolitis (32%), secondary bacterial pneumonia (26 %), and ARDS (21%). Thirty-six patients (77 %) presented with a number of underlying medical conditions. 47% of the patients received mechanical ventilation, and one patient (2%) extracorporeal membrane oxygenation; 19% were treated with the antiviral oseltamivir. 11% had pulmonary sequelae and the mortality rate was 11%, correlating with underlying co-existing chronic conditions and the causative infective agent was A(H1N1)pdm09. It was concluded that this high occurrence was related with underestimation of the pandemic as wel as the post pandemic effects. Hypothetical articulation was formulated for the severity of the infection towards the younger fraction of the population as it is considered obvious that the older fractions of the population develop immunity towards the virus.

These results are supported by more extensive surveillance analyses like for example the ones that monitor total attended "acute respiratory infection" (MAARI) (An der Heiden, 2017). The German physician sentinel is sensitive; however, it requires the development of appropriate modeling techniques to acquire and relate estimates of disease that are attributed to influenza. The data on MAARI and relevant virological results of respiratory samples for 2001/02 until 2014/15 were used. Statistical regression models were constructed to identify potential trends. These influenza-attributable MAARI (iMAARI) estimates were then distributed among the different subtypes of the virological sentinel. The analysis reveals dominance of A(H3), and iMAARI attack rate of the pandemic 2009 (A(H1)pdm09) was 4.9%. The youngest portion of the population again is the most vulnerable, reaching frequently levels up to 15%-20%. Similarly, influenza B affected the age group of 5- to 14-year-old children substantially more than any other age group. This model covers the past but can be extremely valuable in predicting and following disease in the future.

Schmid et al address (Schmid, 2017) a very significant issue for the increased mortality and infection rates in extensive epidemics and pandemics is the so called Influenza vaccine hesitancy. The reluctant uninformed special public groups in high risk they can skyrocket deaths and populate hospitals during the influenza season. This is a global threat and the barriers have been more or less been identified but there are culture barriers, therefore intensive research efforts are constantly developed. This knowledge will eventually bridge the gap, consist the foundation of well educated awareness campaigns and essentially will increase eventually the number of vaccinated individuals. A number of studies analyzing comparatively vaccination, risk groups the general public. Based on this information the knowledge gap is attempted to be mapped sufficiently and the psychological factor is addressed. To address this challenge an intense literature search covering 13 databases for diverse scientific discipline articles was assessed from 2005 to 2016. Emphasis was given to analyze mathematically these articles for a framework based on the Theory of Planned behavior. The majority of the publications were coming from the Americas and Europe. Researchers were studying health care professionals and the general public. The parental decisions for children and their health understudied populations and concepts were also included. A number of barriers were identified for the uptake of the vaccine especially in risk groups. These barriers are mostly psychological and

conceptual as different levels of confidence, convenience, financial calculation and complacency were highlighted. In fact most of these reasons are often related with social status and demographics. It was also considered that the majority of these factors are addressing the uptake vaccine hesitance, they can't provide a rationale for quantitative assessments such as intense or emergent uptake. It became obvious that these studies should be comparative and take under consideration a variety of additional factors, otherwise they will be simply supportive.

Influenza Virus Vaccination in Germany – Results of the »German Health Update« study (GEDA) 2009 (RKI, 2011)

What will be the pivotal factor in influenza infection rates in Germany? All the factors described in this discussion section (environmental temperature, translocation and immigration waves, the enhanced possibility of transfer and occurrence of new recombinant viruses as well as the antiviral resistance patterns) have a significant portion in the resistant patterns, mortality rates, annual influenza epidemics, a large number of lost working hours and severe infections in Germany as well as worldwide (RKI 2010a, 2011). Influenza is seasonal with a season beginning with the new year (January-February) lasting for approximately eight to ten weeks. The preventive influenza consensus, requires vaccination according of course in the annual predominant viruses that are circulating. In Germany, the Standing Committee on Vaccination (STIKO) recommends seasonal influenza vaccinations for special population groups (senior citizens. healthcare workers, pregnant women and underlying diseases) (RKI 2010b). Despite the presence of comprehensive vaccination programs in the majority of the western European countries Unlike several other European countries, in Germany a central vaccination register has not been established. The statistical analysis of vaccinated individuals per annum deploying tools such as telephone surveys, health insurance data and records, as well as commercially available household surveys (e.g. the 2003 microcensus). These elements were the primary calculators to determine state and country rates for vaccination coverage (Blank et al 2009; Blank et al 2008; Wiese-Posselt 2006; Reuss et al 2010; Rehmet et al 2002; Statistisches Bundesamt 2004). If somebody will follow the available datasets, the influenza vaccination rates have not changed significantly since 2005/06 although a rise have been noticed after 2000. The decline in vaccination coverage is more apparent among the specific risk populations in Germany (Blank et al 2009). Is also obvious that the vaccination coverage campaigns

lack objective measurement and metrics to evaluate and optimize if needed. (BZgA 2011). RKI fostered telephonic health survey the "German Health Update" (GEDA) that was conducted by the Department of Epidemiology and Health Reporting (www.rki.de/geda), it was one step in the development of continuous vaccination coverage assessment for everybody and not necessarily in special groups. One comparative advantage when compared with other similar telephonic surveys on influenza vaccination is the size of the sample size as it contains about 21,000 (e. g. Blank et al 2009; Blank et al 2008; Wiese-Posselt 2006). This provides opportunities for classifications regionally as well as for specific groups plus the statistics are compelling, thus analysis related of socio-demographic and socio-economic factors. Subsequently, fostering new vaccination initiatives will be probably one of the most important factors in reducing influenza severity in Germany. This analysis should be viewed in context with existing efforts and health surveys from the RKI (GSTel03 – GSTel07, RKI 2008). Vaccination coverage apparently is a multi factorial health issue and has to be viewed as such.

APPENDIX

A. Abbreviations

ABBREVIATIONS	
ARDS	Acute Respiratory Distress Syndrome
BARDA	Biomedical Advanced Research and Development Authority
CDC	Center of Diseases Control and Prevention
CI	Confidence Interval
CW	Calendar Week
GFT	Google Flu Trends
HPV	Human Papilloma Virus
IAV	Influenza A virus
IBV	Influenza B virus
ICV	Influenza C viruses
ILI	Influenza-Like Illness
IQR	Interquartile Range
IDSA	Infectious Diseases Society of America
IfSG	Infektionsschutzgesetz
MAARI	Medically Attended Acute Respiratory Infection
NAATs	Nucleic Acid Amplification Tests
NAI	Neuraminic Acid Inhibitors
NIC	National Reference Center for Influenza
NP	NasoPharyngeal
NHS	National Health System, UK
PICU	Pediatric Intensive Care Unit
OOH GPCs	Out-of-Our General Physicians Cooperatives
RIDT	Rapid Influenza Detection Tests
RKI	Robert Koch Institute
SIV	Swine Influenza Virus
VPD	Vaccine Preventable Diseases
WHO	World HealthOrganization

B. R code

Code in "R":

```
#data states:
a<-read.csv("C:\\Users\\MY
PC\\Desktop\\dataflu.csv",sep=";",header=TRUE,dec=".")
a
names(a)<-
c("2000/01","2001/02","2002/03","2003/04","2004/05","2005/06","2006/07",
"2007/08","2008/09","2009/10","2010/11","2010/11","2011/12","2012/13","2
013/14","2014/15","2015/16")
names(a)
dates<-
c("2000","2001","2002","2003","2004","2005","2006","2007","2008","2009",
"2010","2011","2012","2013","2014","2015")
dates<-as.numeric(dates)
dates
Baden_Wrttemberg<-as.numeric(a[1,][2:17])
Baden_Wrttemberg
plot(dates,Baden_Wrttemberg,type="l")
Bavaria<-as.numeric(a[2,][2:17])
plot(dates,Bavaria,type='l')
Berlin<-as.numeric(a[3,][2:17])
plot(dates,Berlin,type='l')
Brandeburg<-as.numeric(a[4,][2:17])
plot(dates,Brandeburg,type='l')
Bremen<-as.numeric(a[5,][2:17])
plot(dates,Bremen,type='l')
Hamburg<-as.numeric(a[6,][2:17])
plot(dates,Hamburg,type='l')
Hesse<-as.numeric(a[7,][2:17])
plot(dates,Hesse,type='l')
Mecklenburg_Vorpommern<-as.numeric(a[8,][2:17])
plot(dates,Mecklenburg_Vorpommern,type='l')
Lower_Saxony<-as.numeric(a[9,][2:17])
plot(dates,Lower_Saxony,type='l')

North_Rhine_Westphalia<-as.numeric(a[10,][2:17])
plot(dates,North_Rhine_Westphalia,type='l')
Rhineland_Palatinate<-as.numeric(a[11,][2:17])
plot(dates,Rhineland_Palatinate,type='l')
Saarland<-as.numeric(a[12,][2:17])
plot(dates,Saarland,type='l')
Saxony<-as.numeric(a[13,][2:17])
plot(dates,Saxony,type='l')
Saxony_Anhalt<-as.numeric(a[14,][2:17])
plot(dates,Saxony_Anhalt,type='l')
Schleswig_Holstein<-as.numeric(a[15,][2:17])
plot(dates,Schleswig_Holstein,type='l')
Thuringia<-as.numeric(a[16,][2:17])
```

```
plot(dates,Thuringia,type='l')
boxplot(Baden_Wrttemberg,Bavaria,Berlin,Brandeburg,Bremen,Hamburg,Hes
se,Mecklenburg_Vorpommern,Lower_Saxony,North_Rhine_Westphalia,Rhine
land_Palatinate,Saarland,Saxony,Saxony_Anhalt,Schleswig_Holstein,Thuring
ia,names=c('Baden','Bavaria','Berlin','Brandeburg','Bremen','Hamburg','Hesse',
'Mecklenburg','Lower_Saxony','North_Rhine_Westphalia','Rhineland','Saarlan
d','Saxony','Saxony_Anhalt','Schleswig','Thuringia'))
boxplot(Baden_Wrttemberg,Bavaria,Berlin,Brandeburg,Bremen,Hamburg,Hes
se,Mecklenburg_Vorpommern,Lower_Saxony,North_Rhine_Westphalia,Rhine
land_Palatinate,Saarland,Saxony,Saxony_Anhalt,Schleswig_Holstein,Thuring
ia)
summary(a)
summary(Berlin)
summary(Baden_Wrttemberg)
summary(Bavaria)
summary(Brandeburg)
summary(Bremen)
summary(Hamburg)
summary(Hesse)
summary(Mecklenburg_Vorpommern)
summary(Lower_Saxony)
summary(North_Rhine_Westphalia)
summary(Rhineland_Palatinate)
summary(Saarland)
summary(Saxony)
summary(Saxony_Anhalt)
summary(Schleswig_Holstein)
summary(Thuringia)

dim(a)
A=a[,-1]
Names=a[,1]
Names
t(A)
c(t(A))
Names<-as.factor(rep(Names,each=16))
Y=c(t(A))
NData=data.frame(Y,Names)
install.packages("ggplot2")
library(ggplot2)
ggplot(NData, aes(Y, fill = Names)) + geom_density(alpha = 0.2)
npk.aov <- aov(NData[,1] ~ NData[,2]) # test anova
summary(npk.aov)
kruskal.test(NData[,1] ~ NData[,2]) # kruskal_wallis test boxplot(NData[,1] ~
NData[,2])
```

```
Dataflu<-read.csv("C:/Users/Dimitra/Desktop/dataflu.csv", sep=";")

StatesNam<-Dataflu[,1]

Dataflu<-Dataflu[,-1]

ANDataFlu=data.frame(Cases=c(t(Dataflu)),State=rep(StatesNam,each=16),Y
ear=rep(2000:2015,times=16))

anova(lm(Cases~State, ANDataFlu))
anova(lm(Cases~ Year, ANDataFlu))
anova(lm(Cases~ State+Year, ANDataFlu))

library(Hmisc)

myerrorbar(ANDataFlu$Cases,ANDataFlu$State,horizontal=T)
myerrorbar(ANDataFlu$Cases,ANDataFlu$Year,horizontal=F)

#Data_age-rates

Data<-read.csv(file.choose(),sep="",header=TRUE,dec=".")
Data
colnames(Data)<-c(2000:2015)
length(c(2000:2015))
rownames(Data)<-c("0-4","5-14","15-44","45-64","65+")
Data<-t(Data)
range(c(Data))
agegroup=rep(c("0-4","5-14","15-44","45-64","65+"),each=16)
agegroup<-factor(agegroup, levels = c("0-4","5-14","15-44","45-64","65+") )
df=data.frame(y=c(Data),agegroup=agegroup,year=rep(c(2000:2015),5))
ggplot(data = df, aes(x=year, y=y)) + geom_line(aes(colour=agegroup))
plot(Data[,1],type="l",ylim=c(0,35000))
lines(Data[,2],type="l",col=2)
lines(Data[,3],type="l",col=3)
lines(Data[,4],type="l",col=4)
lines(Data[,5],type="l",col=5)



library(ggplot2)

Rates<-matrix(
c(8.14,16.54,78.6,33.96,74.55,20.72,176.75,81.73,216.54,326.74,243.44,86.4
2,384.69,47.97,326.14,391.35,
142.43,150.97,160.85,170.57,183.54,193.61,210.46,221.97,238.49,254.17,155
.86,149.03,175.59,158.32,228.7,265.03,
39.14,41.55,44.32,47.19,50.81,54.48,59.63,65.05,71.86,78.6,48.09,47.57,57.5
5,54.01,77.23,77.3,
23.79,25.32,27.05,28.88,31.19,33.58,36.83,40.39,44.77,49.41,45.85,49.29,60.
```

```
07,55.56,79.73,59.33,
13.16,14.02,14.98,15.99,17.23,18.43,20.2,22.09,24.6,27.3,30.37,35.21,35.21,
44.41,63.7,34.22)
,ncol=16,,nrow=5,byrow=TRUE)

colnames(Rates)<-
c(2000,2001,2002,2003,2004,2005,2006,2007,2008,2009,2010,2011,2012,201
3,2014,2015)

rownames(Rates)<-c("0-4","5-14","15-44","45-64","65+")

Rates<-t(Rates)

range(c(Rates))

agegroup=rep(c("0-4","5-14","15-44","45-64","65+"),each=16)
agegroup<-factor(agegroup, levels = c("0-4","5-14","15-44","45-64","65+") )

df=data.frame(y=c(Rates),agegroup=agegroup,year=rep(c(2000:2015),5))
ggplot(data = df, aes(x=year, y=y)) + geom_line(aes(colour=agegroup))

plot(Rates[,1],type="l",ylim=c(0,400))
lines(Rates[,2],type="l",col=2)
lines(Rates[,3],type="l",col=3)
lines(Rates[,4],type="l",col=4)
lines(Rates[,5],type="l",col=5)

hist(Rates[,1])
hist(Rates[,2])
hist(Rates[,3])
hist(Rates[,4])
hist(Rates[,5])

HistData<-data.frame( c(Rates), agegroup)
ggplot(HistData, aes(c.Rates., fill = agegroup)) + geom_density(alpha = 0.2)
```

#ACP model

```
Data <- read.csv(file.choose(), sep=";")
dim(Data)
Data$value[is.na(Data$value)]<-0
head(Data)
summary(Data)
trend=c()
sin12=c()
cos12=c()
```

```
for (i in 1:max(Data$NewVar)){
    trend[Data$NewVar==i]<-i/848
}

for (i in 1:max(Data$NewVar)){
    cos12[Data$NewVar==i]<-cos((2*pi*i)/12)
}

for (i in 1:max(Data$NewVar)){
    sin12[Data$NewVar==i]<-sin((2*pi*i)/12)
}

Data$trend<-trend
Data$cos12<-cos12
Data$sin12<-sin12
Data<-Data[,-c(1,4,6,7)]
head(Data);dim(Data)

### poisson model
library(acp)
model<-
acp(value/10~as.factor(AgeGroup)+as.factor(State)+trend+cos12+sin12,data=
Data, family="poisson")
summary(model)$AIC
Data<-data.frame(Data)

Data$value2<-Data$value+1

mod110 <-
acp(value2/10~as.factor(AgeGroup)+as.factor(State)+trend+cos12+sin12,data
=Data, p = 1 ,q = 0)
summary(mod110)$AIC

mod101 <-
acp(value2/10~as.factor(AgeGroup)+as.factor(State)+trend+cos12+sin12,data
=Data, p = 0 ,q = 1)
summary(mod101 )$AIC

mod120 <-
acp(value2/10~as.factor(AgeGroup)+as.factor(State)+trend+cos12+sin12,data
=Data, p = 2 ,q = 0)
summary(mod120 )$AIC
summary(mod120 )

mod102 <-
acp(value2/10~as.factor(AgeGroup)+as.factor(State)+trend+cos12+sin12,data
=Data, p = 0 ,q = 2)
summary(mod102 )$AIC

mod11 <-
```

```
acp(value2/10~as.factor(AgeGroup)+as.factor(State)+trend+cos12+sin12,data
=Data, p = 1 ,q = 1)
summary(mod11)$AIC

mod12 <-
acp(value2/10~as.factor(AgeGroup)+as.factor(State)+trend+cos12+sin12,data
=Data, p = 1 ,q = 2)
summary(mod12)$AIC

mod21 <-
acp(value2/10~as.factor(AgeGroup)+as.factor(State)+trend+cos12+sin12,data
=Data, p = 2 ,q = 1)
summary(mod21)$AIC
summary(mod21)


plot(fitted.values(mod120),type="l",ylim=c(0,50))
lines(log(Data$value2),col="red",type="l")
```

#ZIP model

```
library(pscl)
library(boot)
library(nortest)
library(Hmisc)
library(lmtest)
library(plyr)
library(car)

Data <- read.csv(file.choose(), sep=";")
x=sample(1:67840,67840)
length(unique(x))
Data=Data[x,]
dim(Data)
Data$value[is.na(Data$value)]<-0
head(Data)
summary(Data)
Period<-rep("Hot_Period",dim(Data)[1])
Period[Data$Week %in% c(1:15,45:53)]<-"Cold_Period"
Data$Period<-Period
mean(Data$value[Data$Period=="Cold_Period"])
mean(Data$value[Data$Period=="Hot_Period"])
table(Data$Period)
Data<-Data[,c(2,3,5,6,9)]
str(Data);summary(Data)
Data$Year<-Data$Year-2000
ZIPmodel <- zeroinfl(floor(value/10) ~ State+AgeGroup+Year| Period , data
= Data)
summary(ZIPmodel)
InDOnes=exp(confint(ZIPmodel)[,1])<1 & exp(confint(ZIPmodel)[,2])>=1
```

```
cbind(exp(cbind(Est_Coef = coef(ZIPmodel), confint(ZIPmodel))))
dwtest(ZIPmodel)

sum(abs(resid(ZIPmodel) > 2))
breaks <- seq(-0.5,20.5,1)
par(mfrow=c(2,1))
hist(floor(Data$value/10))
hist(fitted(ZIPmodel ))

ZIPmodel2 <- zeroinfl(floor(value/10) ~ State+AgeGroup+Year+Period |
Period , data = Data)
summary(ZIPmodel2 )
cbind(exp(cbind(Est_Coef = coef(ZIPmodel2 ), confint(ZIPmodel2 ))))

I<-which(Data$State=="Schleswig-Holstein" | Data$State=="Hesse" |
Data$State=="Bremen" | Data$State=="North Rhine-Westphalia" |
Data$State=="Saarland" )
ZIPmodel3 <- zeroinfl(floor(value/10) ~ State+AgeGroup+Year+Period |
Period , data = Data[-I,])
summary(ZIPmodel3 )
cbind(exp(cbind(Est_Coef = coef(ZIPmodel3 ), confint(ZIPmodel3 ))))

Data <- read.csv(file.choose(), sep=";")
Data$value[is.na(Data$value)]<-0
dim(Data)
head(Data)
summary(Data)
table(Data$AgeGroup)
NewValue<-sapply(split(Data$ value,Data$NewVar),mean,na.rm=TRUE)
plot(1:848,NewValue,type="l")
install.packages((gplots))
library(gplots)
library(Hmisc)

#ERROR BAR

library(Hmisc)
myerrorbar<-function(x,y, horizontal=F){
        a<-0.05
        sdata <- split(x,y)
        means <- sapply( sdata,mean,na.rm=TRUE )
        sds <- sapply( split(x,y), sd,na.rm=TRUE  )
        ns <- table(y)
        LB <- means + qnorm( a/2 ) * sds /sqrt(ns)
        UB <- means + qnorm( 1-a/2 ) * sds /sqrt(ns)
        nlev <- nlevels(y)
        if (horizontal) { errbar( levels(y), means, UB, LB, las=2 )
                par(las=2)
                } else {
              par(las=2)
```

```
                                errbar( 1:nlev, means, UB, LB, xlim=c(0,nlev+1),
axes=F, xlab='',las=2 )
                                axis(2,las=2)
                                axis(1, at=0:(nlev+1), labels=c('',levels(y),''))
                               }

}

#AGE GROUP 0-4
Data04<-subset(Data,Data$AgeGroup=="00-04");head(Data04);dim(Data04)
NewValue<-sapply(split(Data04$ value,Data04$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(Data04$ Year,Data04$NewVar),mean,na.rm=TRUE)
Dat04<-data.frame(Cases=NewValue,Year=NewYear)
plot(1:848,NewValue,type="l")
plotmeans(Dat04$Cases~Dat04$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(Dat04$Cases,as.factor(Dat04$Year))

#AGE GROUP 5-14
Data514<-
subset(Data,Data$AgeGroup=="05.14");head(Data514);dim(Data514)
NewValue<-sapply(split(Data514$
value,Data514$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(Data514$
Year,Data514$NewVar),mean,na.rm=TRUE)
Data514<-data.frame(Cases=NewValue,Year=NewYear)
plot(1:848,NewValue,type="l")
plotmeans(Data514$Cases~Data514$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(Data514$Cases,as.factor(Data514$Year))



#AGE GROUP 15-44
1Data1544<-subset(Data,Data$AgeGroup=="15-
44");head(Data1544);dim(Data1544)
NewValue<-sapply(split(Data1544$
value,Data1544$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(Data1544$
Year,Data1544$NewVar),mean,na.rm=TRUE)
Data1544<-data.frame(Cases=NewValue,Year=NewYear)
plot(1:848,NewValue,type="l")
plotmeans(Data1544$Cases~Data1544$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(Data1544$Cases,as.factor(Data1544$Year))

#AGE GROUP 45-64
Data4564<-subset(Data,Data$AgeGroup=="45-
64");head(Data4564);dim(Data4564)
NewValue<-sapply(split(Data4564$
```

```
value,Data4564$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(Data4564$
Year,Data4564$NewVar),mean,na.rm=TRUE)
Data4564<-data.frame(Cases=NewValue,Year=NewYear)
plot(1:848,NewValue,type="l")
plotmeans(Data4564$Cases~Data4564$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(Data4564$Cases,as.factor(Data4564$Year))

#AGE GROUP 65+
Data65p<-
subset(Data,Data$AgeGroup=="65+");head(Data65p);dim(Data65p)
NewValue<-sapply(split(Data65p$
value,Data65p$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(Data65p$
Year,Data65p$NewVar),mean,na.rm=TRUE)
Data65p<-data.frame(Cases=NewValue,Year=NewYear)
plot(1:848,NewValue,type="l")
plotmeans(Data65p$Cases~Data65p$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(Data65p$Cases,as.factor(Data65p$Year))

#STATES
DataOr<-Data
Ind<-which(Data$State=="Schleswig-Holstein" | Data$State=="Hesse")
Data<-Data[-Ind,]
table(Data$State)

#STATE Baden-Wurttemberg
DataBW<-subset(Data,Data$State=="Baden-
W?rttemberg");head(DataBW);dim(DataBW)
NewValue<-sapply(split(DataBW$
value,DataBW$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataBW$
Year,DataBW$NewVar),mean,na.rm=TRUE)
DataBW<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataBW$Cases~DataBW$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(DataBW$Cases,as.factor(DataBW$Year))

#STATE Bavaria
DataBVR<-
subset(Data,Data$State=="Bavaria");head(DataBVR);dim(DataBVR)
NewValue<-sapply(split(DataBVR$
value,DataBVR$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataBVR$
Year,DataBVR$NewVar),mean,na.rm=TRUE)
DataBVR<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataBVR$Cases~DataBVR$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
```

```
myerrorbar(DataBVR$Cases,as.factor(DataBVR$Year))

#STATE Berlin
DataBrl<-subset(Data,Data$State=="Berlin");head(DataBrl);dim(DataBrl)
NewValue<-sapply(split(DataBrl$
value,DataBrl$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataBrl$ Year,DataBrl$NewVar),mean,na.rm=TRUE)
DataBrl<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataBrl$Cases~DataBrl$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(DataBrl$Cases,as.factor(DataBrl$Year))

#STATE Brandenburg
DataBrnd<-
subset(Data,Data$State=="Brandenburg");head(DataBrnd);dim(DataBrnd)
NewValue<-sapply(split(DataBrnd$
value,DataBrnd$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataBrnd$
Year,DataBrnd$NewVar),mean,na.rm=TRUE)
DataBrnd<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataBrnd$Cases~DataBrnd$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(DataBrnd$Cases,as.factor(DataBrnd$Year))

#STATE Bremen
DataBRmn<-
subset(Data,Data$State=="Bremen");head(DataBRmn);dim(DataBRmn)
NewValue<-sapply(split(DataBRmn$
value,DataBRmn$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataBRmn$
Year,DataBRmn$NewVar),mean,na.rm=TRUE)
DataBRmn<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataBRmn$Cases~DataBRmn$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(DataBRmn$Cases,as.factor(DataBRmn$Year))



#STATE  Hamburg
DataHmrg<-
subset(Data,Data$State=="Hamburg");head(DataHmrg);dim(DataHmrg)
NewValue<-sapply(split(DataHmrg$
value,DataHmrg$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataHmrg$
Year,DataHmrg$NewVar),mean,na.rm=TRUE)
DataHmrg<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataHmrg$Cases~DataHmrg$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(DataHmrg$Cases,as.factor(DataHmrg$Year))
```

#STATE Lower Saxony
```
DataLS<-subset(Data,Data$State=="Lower
Saxony");head(DataLS);dim(DataLS)
NewValue<-sapply(split(DataLS$ value,DataLS$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataLS$ Year,DataLS$NewVar),mean,na.rm=TRUE)
DataLS<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataLS$Cases~DataLS$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(DataLS$Cases,as.factor(DataLS$Year))
```

#STATE Mecklenburg-Vorpommern
```
DataMV<-subset(Data,Data$State=="Mecklenburg-
Vorpommern");head(DataMV);dim(DataMV)
NewValue<-sapply(split(DataMV$
value,DataMV$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataMV$
Year,DataMV$NewVar),mean,na.rm=TRUE)
DataMV<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataMV$Cases~DataMV$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(DataMV$Cases,as.factor(DataMV$Year))
```

#STATE North Rhine-Westphalia
```
DataNRW<-subset(Data,Data$State=="North Rhine-
Westphalia");head(DataNRW);dim(DataNRW)
NewValue<-sapply(split(DataNRW$
value,DataNRW$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataNRW$
Year,DataNRW$NewVar),mean,na.rm=TRUE)
DataNRW<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataNRW$Cases~DataNRW$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(DataNRW$Cases,as.factor(DataNRW$Year))
```

#STATE Rhineland-Palatinate
```
DataRPl<-subset(Data,Data$State=="Rhineland-
Palatinate");head(DataRPl);dim(DataRPl)
NewValue<-sapply(split(DataRPl$
value,DataRPl$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataRPl$
Year,DataRPl$NewVar),mean,na.rm=TRUE)
DataRPl<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataRPl$Cases~DataRPl$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(DataRPl$Cases,as.factor(DataRPl$Year))
```

#STATE Saarland
```
DataSaaRld<-
subset(Data,Data$State=="Saarland");head(DataSaaRld);dim(DataSaaRld)
```


```
NewValue<-sapply(split(DataSaaRld$
value,DataSaaRld$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataSaaRld$
Year,DataSaaRld$NewVar),mean,na.rm=TRUE)
DataSaaRld<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataSaaRld$Cases~DataSaaRld$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(DataSaaRld$Cases,as.factor(DataSaaRld$Year))
```

#STATE Saxony

```
DataSxn<-subset(Data,Data$State=="Saxony");head(DataSxn);dim(DataSxn)
NewValue<-sapply(split(DataSxn$
value,DataSxn$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataSxn$
Year,DataSxn$NewVar),mean,na.rm=TRUE)
DataSxn<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataSxn$Cases~DataSxn$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(DataSxn$Cases,as.factor(DataSxn$Year))
```

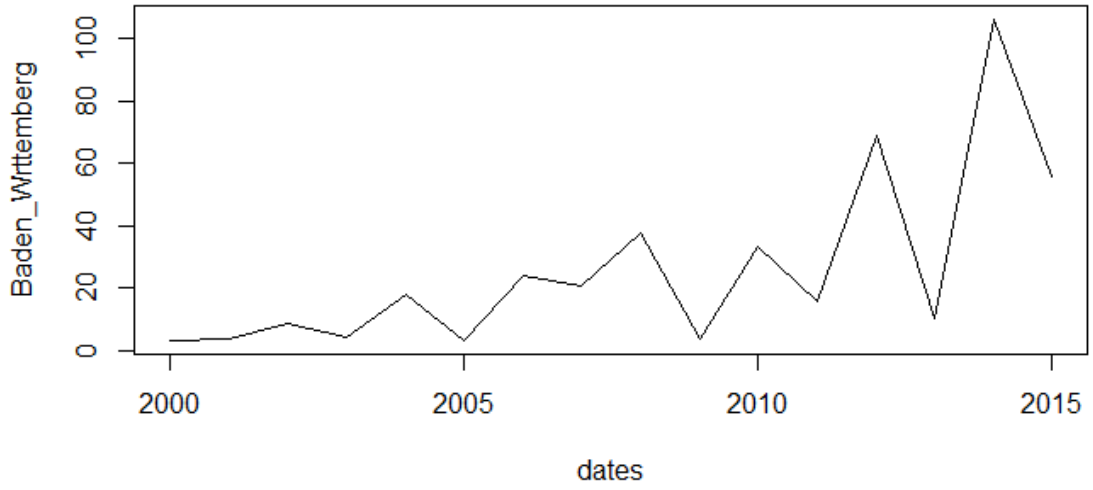
#STATE Saxony-Anhalt

```
DataSxnAn<-subset(Data,Data$State=="Saxony-
Anhalt");head(DataSxnAn);dim(DataSxnAn)
NewValue<-sapply(split(DataSxnAn$
value,DataSxnAn$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataSxnAn$
Year,DataSxnAn$NewVar),mean,na.rm=TRUE)
DataSxnAn<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataSxnAn$Cases~DataSxnAn$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(DataSxnAn$Cases,as.factor(DataSxnAn$Year))
```

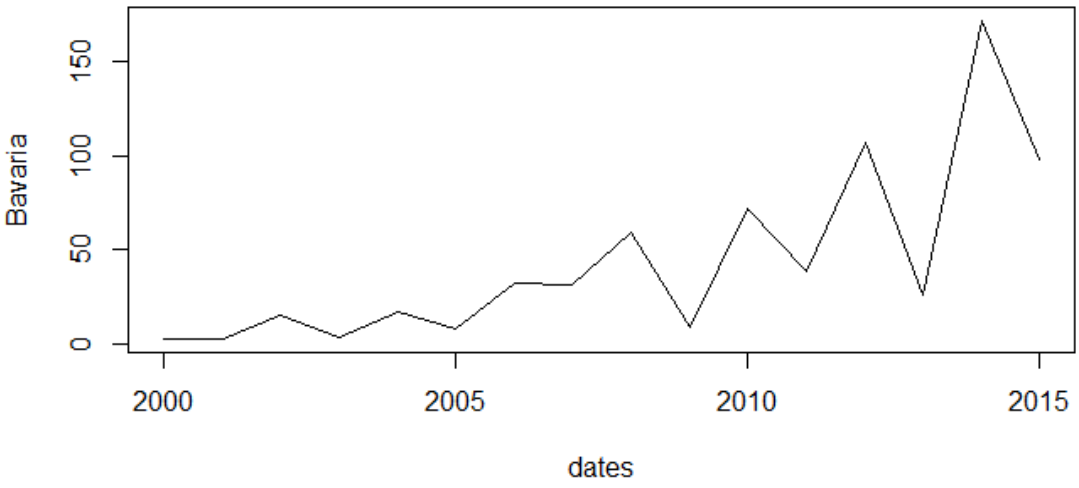
#STATE Thuringia

```
DataThr<-
subset(Data,Data$State=="Thuringia");head(DataThr);dim(DataThr)
NewValue<-sapply(split(DataThr$
value,DataThr$NewVar),sum,na.rm=TRUE)
NewYear<-sapply(split(DataThr$
Year,DataThr$NewVar),mean,na.rm=TRUE)
DataThr<-data.frame(Cases=NewValue,Year=NewYear)
plotmeans(DataThr$Cases~DataThr$Year,
n.label=F,connect=F,xlab="Year",ylab="Cases")
myerrorbar(DataThr$Cases,as.factor(DataThr$Year))
```

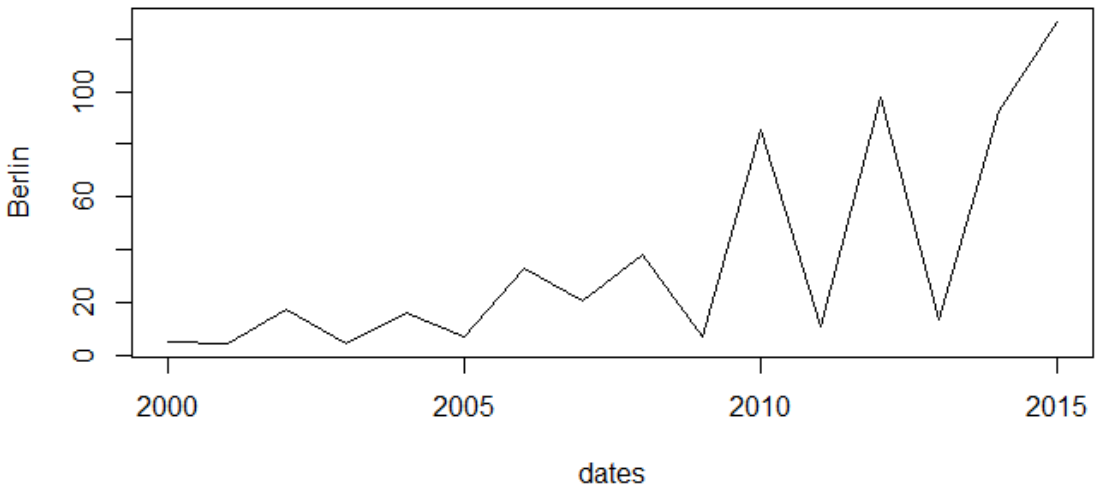
C. **Supplementary figures and tables**



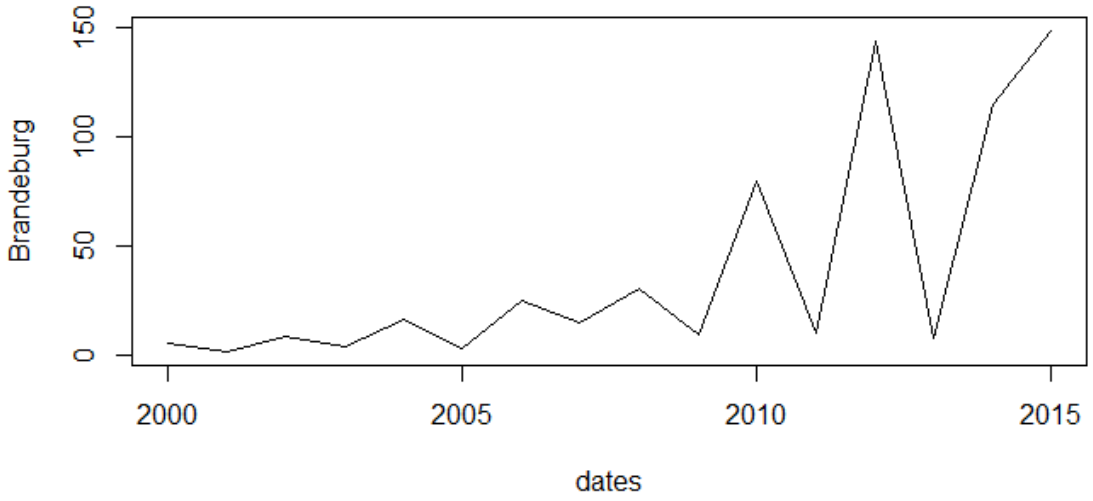
A.



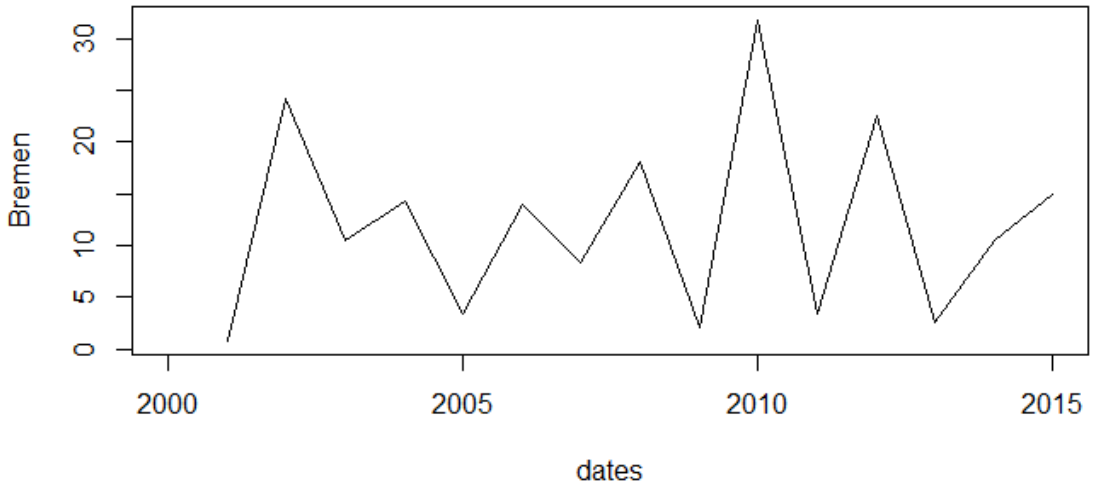
B.



C.



D.



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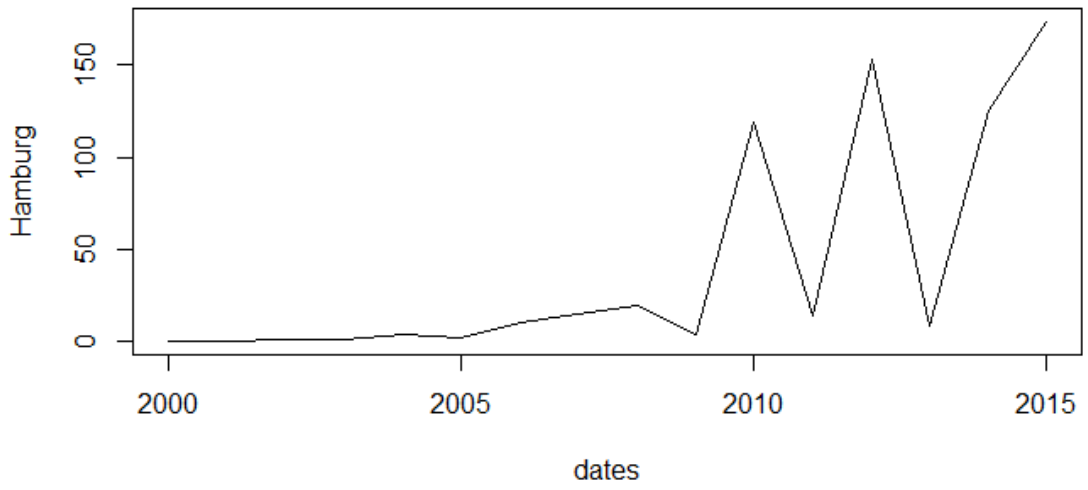

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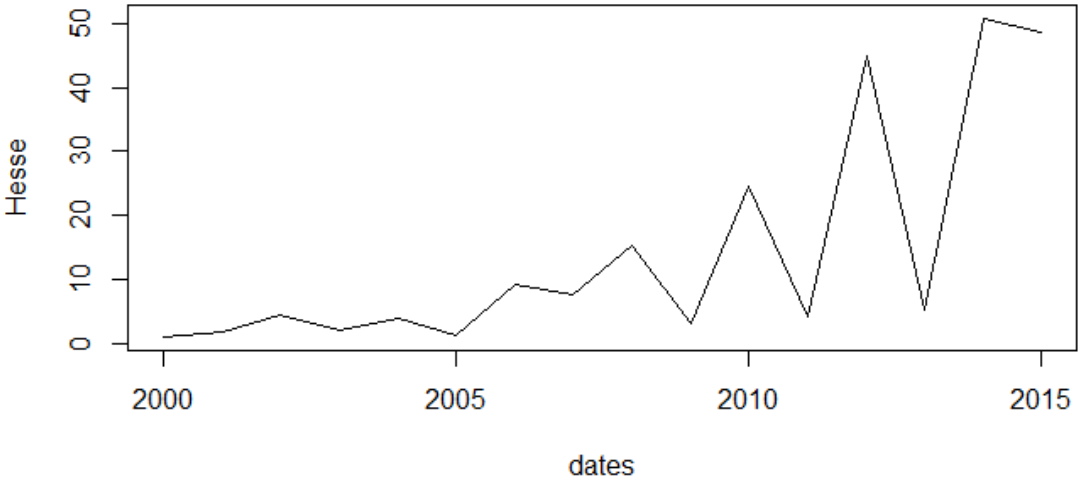
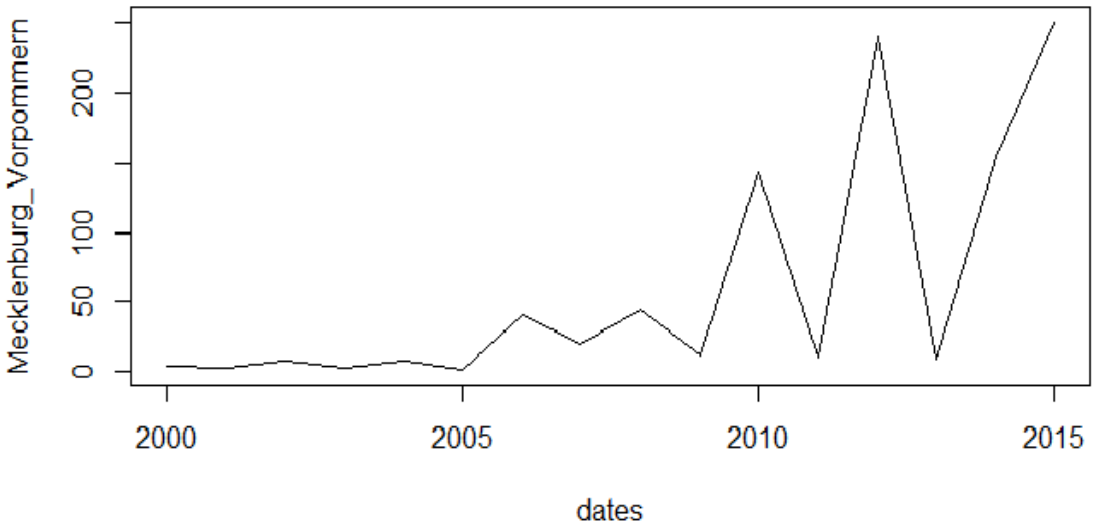
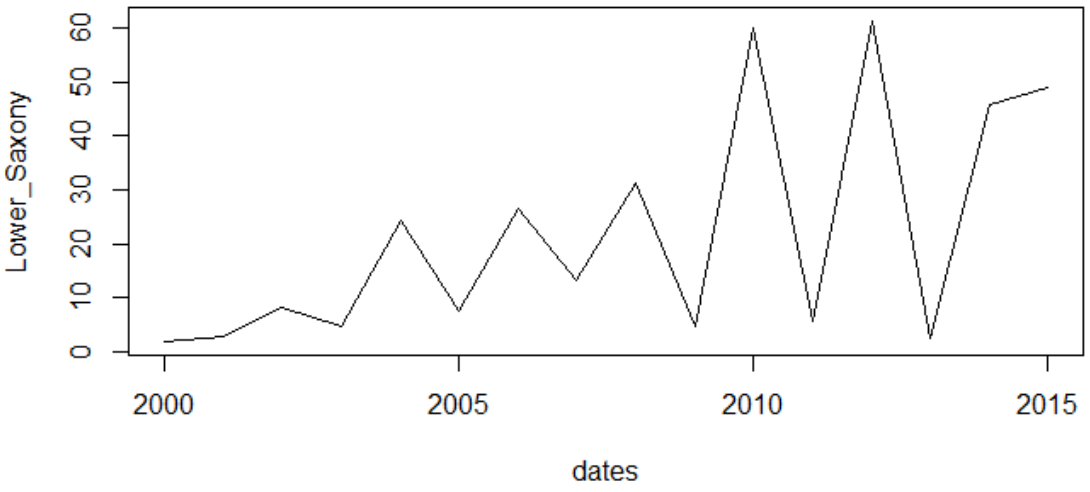


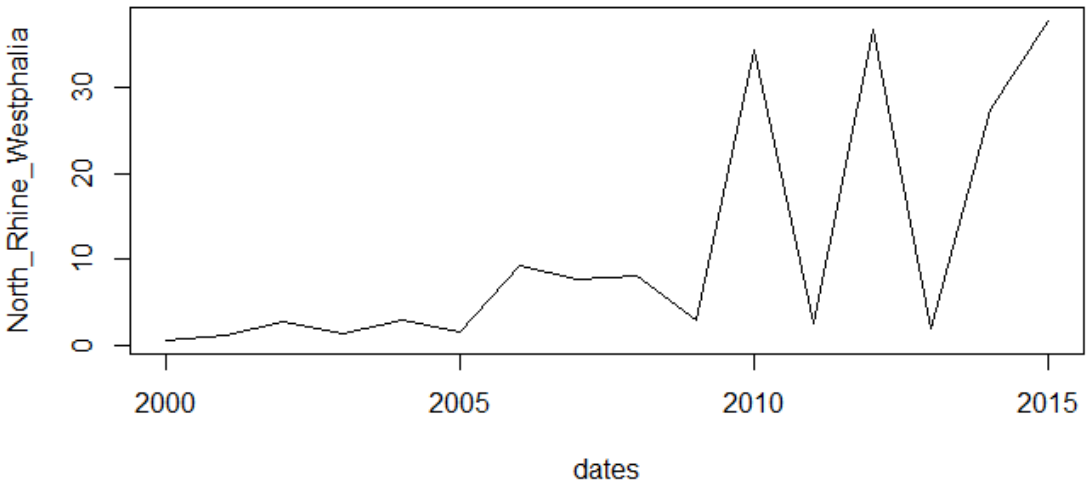
G.



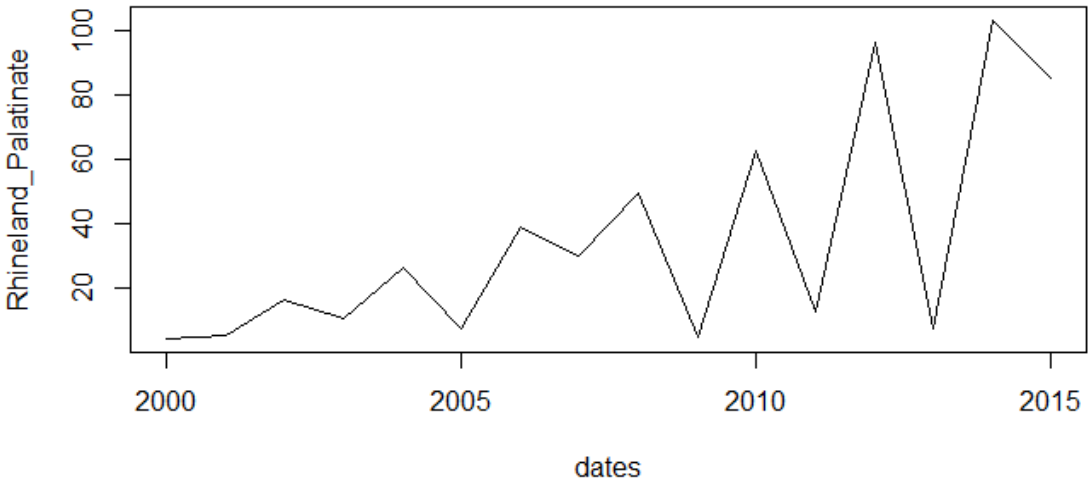
H.



I.



K.



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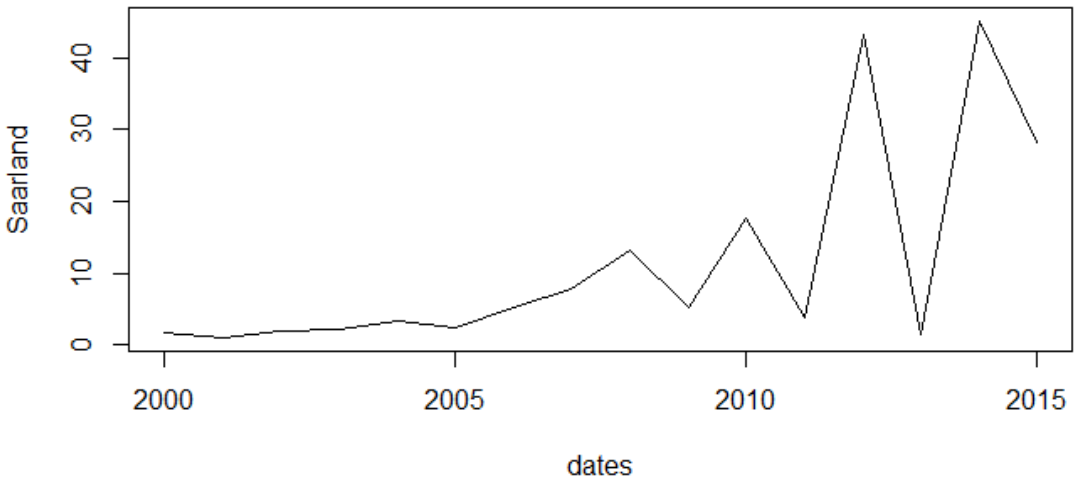
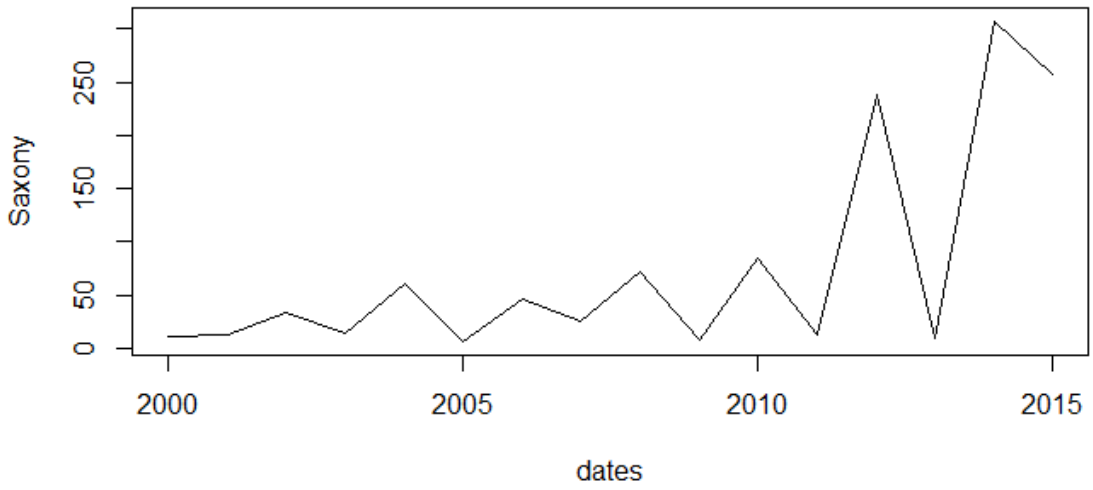


M.



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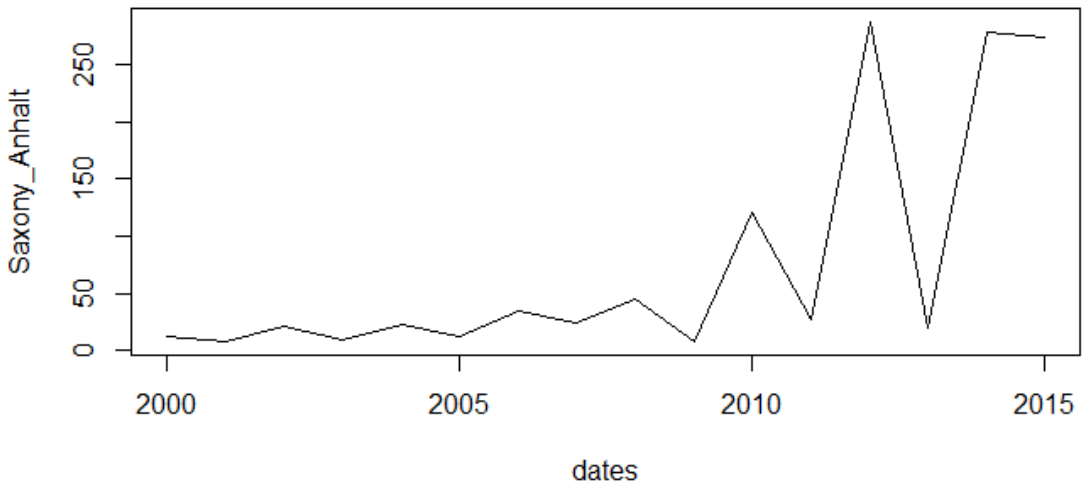
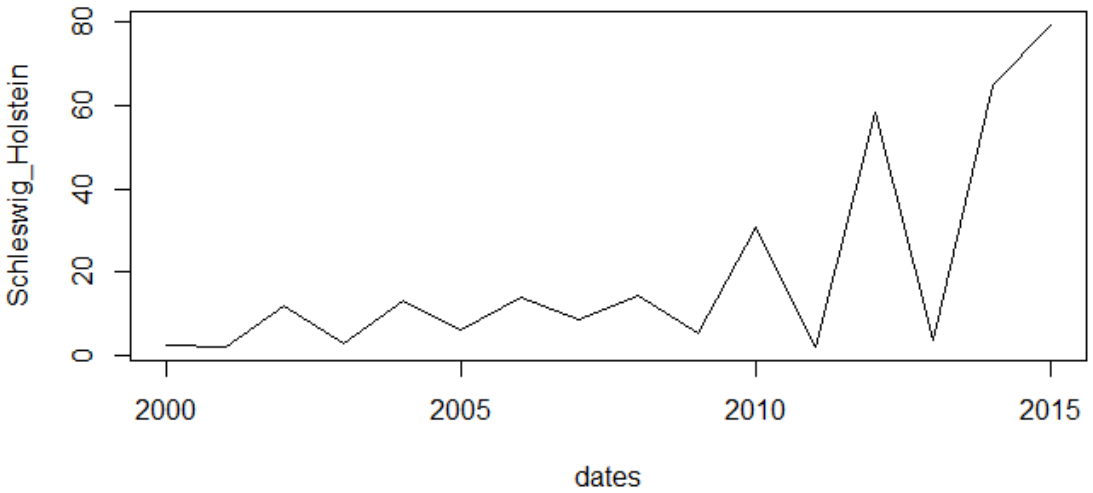
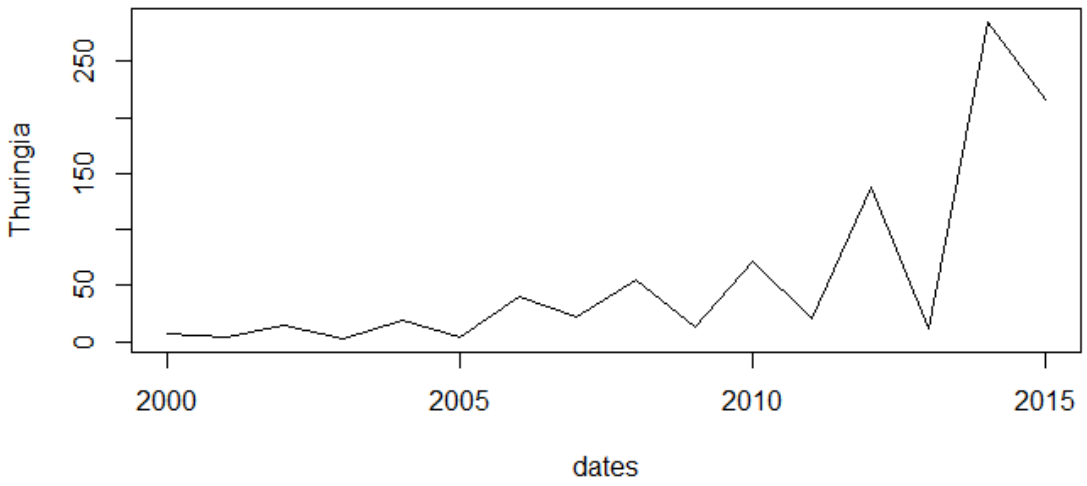


O.



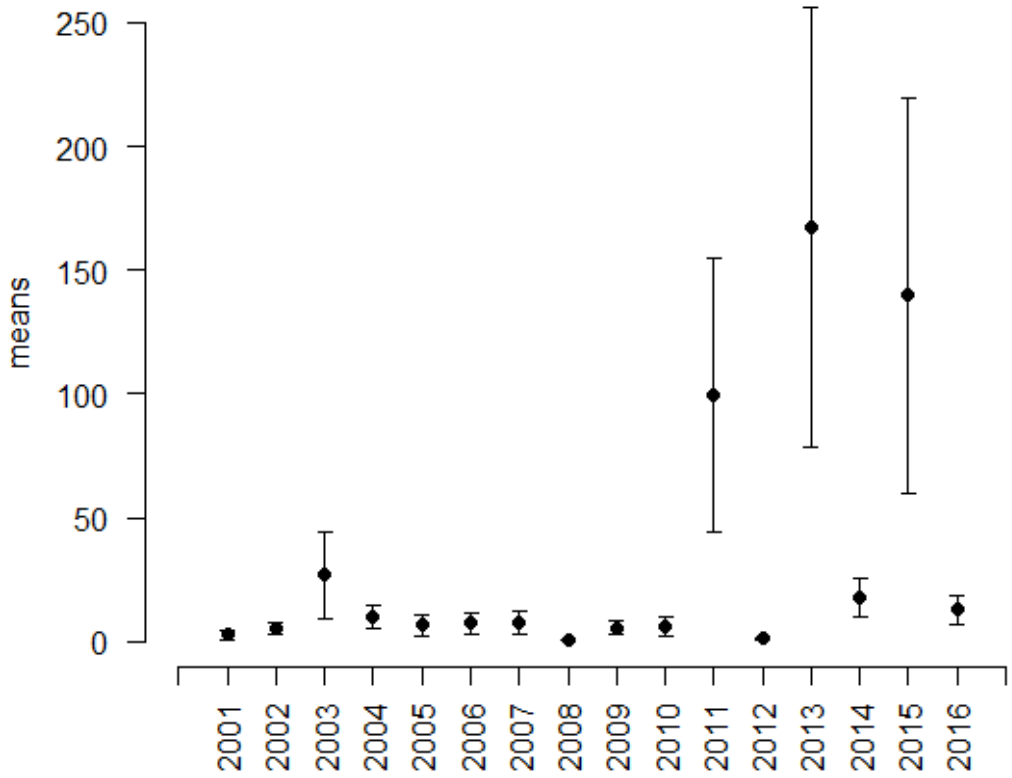
P.



Q.

Figure S1. (A-Q) Cases per federal German state (2000-2015)

A.



B.

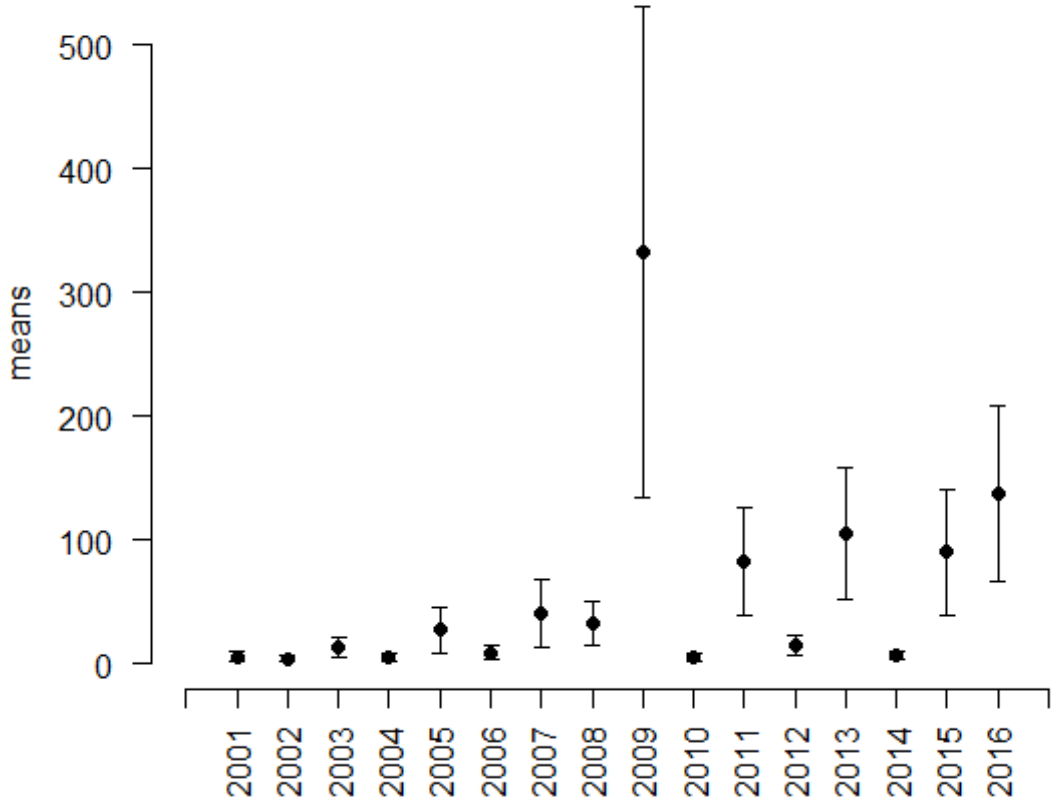
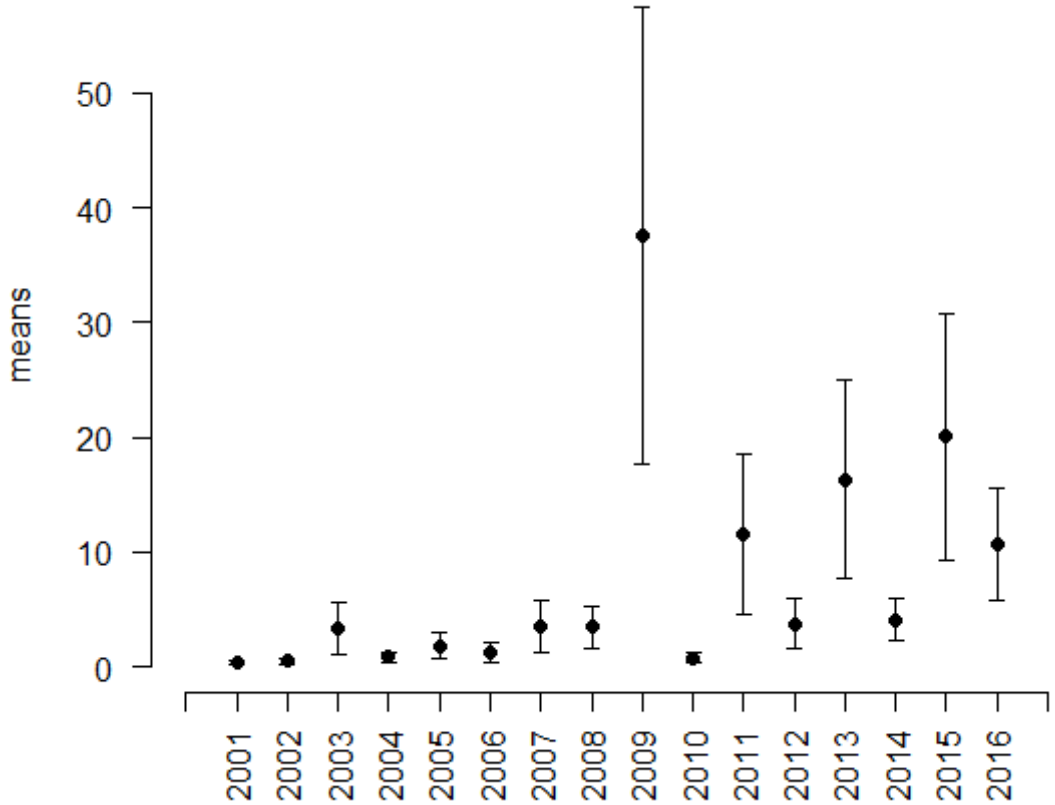


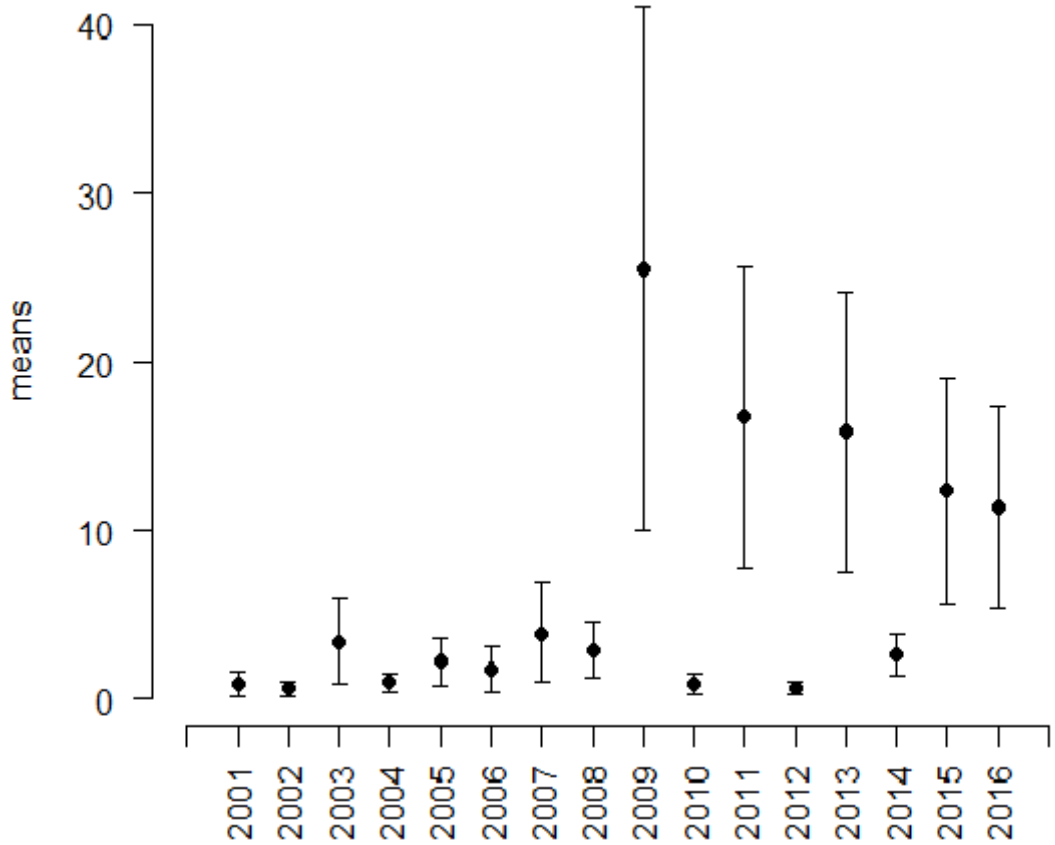
Figure S2 (A-B) Plot of means and errors vs. year for age groups 0-4 (A) and 5-14 (B) respectively.

Bavaria



A.

Berlin



B.

Figure S3 (A-B) Plot of means and errors vs. year for states Bavaria (A) and Berlin (B) respectively.

Table S1	Data 1		
Kruskal-Wallis test			
P value	**0.0015**		
Exact or approximate P value?	**Gaussian Approximation**		
P value summary	****		
Do the medians vary signif. (P < 0.05)	**Yes**		
Number of groups	**16**		
Kruskal-Wallis statistic	**36.40**		
Dunn's Multiple Comparison Test	**Difference in rank sum**	**Significant? P < 0.05?**	**Summary**
Baden-Wÿrttemberg vs Bavaria	**-22.25**	**No**	**ns**
Baden-Wÿrttemberg vs Berlin	**-14.16**	**No**	**ns**
Baden-Wÿrttemberg vs Brandenburg	**-5.406**	**No**	**ns**
Baden-Wÿrttemberg vs Bremen	**22.78**	**No**	**ns**
Baden-Wÿrttemberg vs Hamburg	**21.88**	**No**	**ns**
Baden-Wÿrttemberg vs Hesse	**26.28**	**No**	**ns**
Baden-Wÿrttemberg vs Mecklenburg-Vorpommern	**-5.750**	**No**	**ns**
Baden-Wÿrttemberg vs Lower Saxony	**9.406**	**No**	**ns**
Baden-Wÿrttemberg vs North Rhine-Westphalia	**55.28**	**No**	**ns**
Baden-Wÿrttemberg vs Rhineland-Palatinate	**-18.00**	**No**	**ns**
Baden-Wÿrttemberg vs Saarland	**51.88**	**No**	**ns**
Baden-Wÿrttemberg vs Saxony	**-39.13**	**No**	**ns**
Baden-Wÿrttemberg vs Saxony-Anhalt	**-38.56**	**No**	**ns**
Baden-Wÿrttemberg vs Schleswig-Holstein	**23.56**	**No**	**ns**
Baden-Wÿrttemberg vs Thuringia	**-20.81**	**No**	**ns**
Bavaria vs Berlin	**8.094**	**No**	**ns**
Bavaria vs Brandenburg	**16.84**	**No**	**ns**
Bavaria vs Bremen	**45.03**	**No**	**ns**
Bavaria vs Hamburg	**44.13**	**No**	**ns**
Bavaria vs Hesse	**48.53**	**No**	**ns**
Bavaria vs Mecklenburg-Vorpommern	**16.50**	**No**	**ns**
Bavaria vs Lower Saxony	**31.66**	**No**	**ns**
Bavaria vs North Rhine-Westphalia	**77.53**	**No**	**ns**
Bavaria vs Rhineland-Palatinate	**4.250**	**No**	**ns**
Bavaria vs Saarland	**74.13**	**No**	**ns**
Bavaria vs Saxony	**-16.88**	**No**	**ns**
Bavaria vs Saxony-Anhalt	**-16.31**	**No**	**ns**
Bavaria vs Schleswig-Holstein	**45.81**	**No**	**ns**
Bavaria vs Thuringia	**1.438**	**No**	**ns**
Berlin vs Brandenburg	**8.750**	**No**	**ns**
Berlin vs Bremen	**36.94**	**No**	**ns**
Berlin vs Hamburg	**36.03**	**No**	**ns**
Berlin vs Hesse	**40.44**	**No**	**ns**
Berlin vs Mecklenburg-Vorpommern	**8.406**	**No**	**ns**
Berlin vs Lower Saxony	**23.56**	**No**	**ns**
Berlin vs North Rhine-Westphalia	**69.44**	**No**	**ns**
Berlin vs Rhineland-Palatinate	**-3.844**	**No**	**ns**
Berlin vs Saarland	**66.03**	**No**	**ns**
Berlin vs Saxony	**-24.97**	**No**	**ns**
Berlin vs Saxony-Anhalt	**-24.41**	**No**	**ns**
Berlin vs Schleswig-Holstein	**37.72**	**No**	**ns**
Berlin vs Thuringia	**-6.656**	**No**	**ns**
Brandenburg vs Bremen	**28.19**	**No**	**ns**
Brandenburg vs Hamburg	**27.28**	**No**	**ns**
Brandenburg vs Hesse	**31.69**	**No**	**ns**
Brandenburg vs Mecklenburg-Vorpommern	**-0.3438**	**No**	**ns**
Brandenburg vs Lower Saxony	**14.81**	**No**	**ns**
Brandenburg vs North Rhine-Westphalia	**60.69**	**No**	**ns**

Brandenburg vs Rhineland-Palatinate	**-12.59**	**No**	**ns**
Brandenburg vs Saarland	**57.28**	**No**	**ns**
Brandenburg vs Saxony	**-33.72**	**No**	**ns**
Brandenburg vs Saxony-Anhalt	**-33.16**	**No**	**ns**
Brandenburg vs Schleswig-Holstein	**28.97**	**No**	**ns**
Brandenburg vs Thuringia	**-15.41**	**No**	**ns**
Bremen vs Hamburg	**-0.9063**	**No**	**ns**
Bremen vs Hesse	**3.500**	**No**	**ns**
Bremen vs Mecklenburg-Vorpommern	**-28.53**	**No**	**ns**
Bremen vs Lower Saxony	**-13.38**	**No**	**ns**
Bremen vs North Rhine-Westphalia	**32.50**	**No**	**ns**
Bremen vs Rhineland-Palatinate	**-40.78**	**No**	**ns**
Bremen vs Saarland	**29.09**	**No**	**ns**
Bremen vs Saxony	**-61.91**	**No**	**ns**
Bremen vs Saxony-Anhalt	**-61.34**	**No**	**ns**
Bremen vs Schleswig-Holstein	**0.7813**	**No**	**ns**
Bremen vs Thuringia	**-43.59**	**No**	**ns**
Hamburg vs Hesse	**4.406**	**No**	**ns**
Hamburg vs Mecklenburg-Vorpommern	**-27.63**	**No**	**ns**
Hamburg vs Lower Saxony	**-12.47**	**No**	**ns**
Hamburg vs North Rhine-Westphalia	**33.41**	**No**	**ns**
Hamburg vs Rhineland-Palatinate	**-39.88**	**No**	**ns**
Hamburg vs Saarland	**30.00**	**No**	**ns**
Hamburg vs Saxony	**-61.00**	**No**	**ns**
Hamburg vs Saxony-Anhalt	**-60.44**	**No**	**ns**
Hamburg vs Schleswig-Holstein	**1.688**	**No**	**ns**
Hamburg vs Thuringia	**-42.69**	**No**	**ns**
Hesse vs Mecklenburg-Vorpommern	**-32.03**	**No**	**ns**
Hesse vs Lower Saxony	**-16.88**	**No**	**ns**
Hesse vs North Rhine-Westphalia	**29.00**	**No**	**ns**
Hesse vs Rhineland-Palatinate	**-44.28**	**No**	**ns**
Hesse vs Saarland	**25.59**	**No**	**ns**
Hesse vs Saxony	**-65.41**	**No**	**ns**
Hesse vs Saxony-Anhalt	**-64.84**	**No**	**ns**
Hesse vs Schleswig-Holstein	**-2.719**	**No**	**ns**
Hesse vs Thuringia	**-47.09**	**No**	**ns**
Mecklenburg-Vorpommern vs Lower Saxony	**15.16**	**No**	**ns**
Mecklenburg-Vorpommern vs North Rhine-Westphalia	**61.03**	**No**	**ns**
Mecklenburg-Vorpommern vs Rhineland-Palatinate	**-12.25**	**No**	**ns**
Mecklenburg-Vorpommern vs Saarland	**57.63**	**No**	**ns**
Mecklenburg-Vorpommern vs Saxony	**-33.38**	**No**	**ns**
Mecklenburg-Vorpommern vs Saxony-Anhalt	**-32.81**	**No**	**ns**
Mecklenburg-Vorpommern vs Schleswig-Holstein	**29.31**	**No**	**ns**
Mecklenburg-Vorpommern vs Thuringia	**-15.06**	**No**	**ns**
Lower Saxony vs North Rhine-Westphalia	**45.88**	**No**	**ns**
Lower Saxony vs Rhineland-Palatinate	**-27.41**	**No**	**ns**
Lower Saxony vs Saarland	**42.47**	**No**	**ns**
Lower Saxony vs Saxony	**-48.53**	**No**	**ns**
Lower Saxony vs Saxony-Anhalt	**-47.97**	**No**	**ns**
Lower Saxony vs Schleswig-Holstein	**14.16**	**No**	**ns**
Lower Saxony vs Thuringia	**-30.22**	**No**	**ns**
North Rhine-Westphalia vs Rhineland-Palatinate	**-73.28**	**No**	**ns**
North Rhine-Westphalia vs Saarland	**-3.406**	**No**	**ns**
North Rhine-Westphalia vs Saxony	**-94.41**	**Yes**	*****
North Rhine-Westphalia vs Saxony-Anhalt	**-93.84**	**Yes**	*****
North Rhine-Westphalia vs Schleswig-Holstein	**-31.72**	**No**	**ns**
North Rhine-Westphalia vs Thuringia	**-76.09**	**No**	**ns**
Rhineland-Palatinate vs Saarland	**69.88**	**No**	**ns**
Rhineland-Palatinate vs Saxony	**-21.13**	**No**	**ns**
Rhineland-Palatinate vs Saxony-Anhalt	**-20.56**	**No**	**ns**

Rhineland-Palatinate vs Schleswig-Holstein	**41.56**	**No**	**ns**
Rhineland-Palatinate vs Thuringia	**-2.813**	**No**	**ns**
Saarland vs Saxony	**-91.00**	**No**	**ns**
Saarland vs Saxony-Anhalt	**-90.44**	**No**	**ns**
Saarland vs Schleswig-Holstein	**-28.31**	**No**	**ns**
Saarland vs Thuringia	**-72.69**	**No**	**ns**
Saxony vs Saxony-Anhalt	**0.5625**	**No**	**ns**
Saxony vs Schleswig-Holstein	**62.69**	**No**	**ns**
Saxony vs Thuringia	**18.31**	**No**	**ns**
Saxony-Anhalt vs Schleswig-Holstein	**62.13**	**No**	**ns**
Saxony-Anhalt vs Thuringia	**17.75**	**No**	**Ns**
Schleswig-Holstein vs Thuringia	**-44.38**	**No**	**Ns**

Table S2 **Age Groups**

Kruskal-Wallis test	
P value	**< 0.0001**
Exact or approximate P value?	**Gaussian Approximation**
P value summary	*******
Do the medians vary signif. (P < 0.05)	**Yes**
Number of groups	**5**
Kruskal-Wallis statistic	**45.69**

Dunn's Multiple Comparison Test	**Difference in rank sum**	**Significant? P < 0.05?**	**Summary**
0-4 vs 5-14	**-15.59**	**No**	**ns**
0-4 vs 15 – 44	**10.38**	**No**	**ns**
0-4 vs 45-64	**21.22**	**No**	**ns**
0-4 vs >65	**35.72**	**Yes**	*******
5-14 vs 15 – 44	**25.97**	**Yes**	*****
5-14 vs 45-64	**36.81**	**Yes**	*******
5-14 vs >65	**51.31**	**Yes**	*******
15 – 44 vs 45-64	**10.84**	**No**	**ns**
15 – 44 vs >65	**25.34**	**Yes**	*****
45-64 vs >65	**14.50**	**No**	**ns**

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