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Past and present seroprevalence and disease burden estimates of *Toxoplasma gondii* infections in Germany: An appreciation of the role of serodiagnostics

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ABSTRACT

Toxoplasmosis is one of the major foodborne parasitic diseases in Germany, with 49% of its population chronically infected with its causative agent, *Toxoplasma gondii*. Although the acute disease is usually benign in immunocompetent individuals, it is a threat for immunocompromised patients as well as for fetuses of seronegative mothers. As a result of infection, congenital and ocular toxoplasmosis can have serious lifelong consequences. Here I will highlight the epidemiologic situation, from its past in the two separate parts of Germany, to its unification 30 years ago and up to the present day. The main identified risk factor for infection in Germany is thought to be the consumption of undercooked or raw meat or sausages. However, the relative impact of this risky eating habit as well as that of other risk factors are changing and are discussed and compared to the situation in the Netherlands. Finally, the importance of robust and efficient high-throughput serological assays for obtaining reliable epidemiological data, on which public health decisions can be made, is highlighted. The potential of bead-based multiplex assays, which allow the incorporation of multiple antigens with different analytical properties and thus yield additional information, are described in this context. It illustrates the interdependence of new analytic assay developments and sound epidemiology, a foundation that decades-old data from Germany did not have.

1. Introduction to *Toxoplasma gondii* and toxoplasmosis

The intracellular protozoan parasite *Toxoplasma gondii,* causing acute toxoplasmosis, is one of the most widespread pathogens, which is usually never eliminated from an infected host. An estimated 25% of the human population have been in contact with this pathogen (Molan et al., 2019). The success of this zoonotic, single-celled apicomplexan parasite is due to its very large host range (all warm-blooded animals) and multiple modes of infection. It has three infectious stages, the so-called tachyzoites, bradyzoites and sporozoites (Smith et al., 2021). Tachyzoites are the fast-replicating form, responsible for the dissemination once the parasite has reached its host. They can cause congenital infection. The bradyzoite stage is formed after differentiation from tachyzoites within so-called tissues cysts, and reflects the chronic stage of the infection. The ingestion of tissue cysts is probably the most frequent way an omnivorous or carnivorous host becomes infected. Being present in raw or undercooked meat, they can survive the stomach passage, and bradyzoites then infect the host via the intestinal epithelium and disseminate as tachyzoites (Almeria and Dubey, 2021). However, also herbivores get infected via the third infectious stage, sporozoites, that are released from sporulated oocysts and also enter the host via ingestion. Oocysts are the sexual form of *T. gondii* and are only formed in cats and other felidae. Millions of oocysts are shed by a single infected cat, which can survive for extended times (several months) in the environment, thus posing a constant thread for infection, also for humans via contaminated water or food (Shapiro et al., 2019).

Almost half of the German adult population has at least once been infected with the protozoan parasite *T. gondii* (Pleyer et al., 2019; Wilking et al., 2016). The national seroprevalence is thus one of the highest in the world. Toxoplasmosis is usually relatively benign in

Abbreviations: BBMA, bead-based multiplex assay; CT, congenital toxoplasmosis; DALY, disability-adjusted life years; DAT, direct agglutination test; ELFA, enzyme-linked fluorescent assay; ELISA, enzyme-linked immunosorbent assay; FRG, Federal Republic of Germany; GDR, German Democratic Republic; GPI, glycosylphosphatidylinositol; ICD-10, 10th revision of the International Statistical Classification of Diseases; LAT, latex agglutination test; OT, ocular toxoplasmosis; SAG1, surface antigen 1; SAG2A, surface antigen 2A; SFDT, Sabin-Feldman dye test.

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immunocompetent individuals, causing flu-like symptoms and swollen lymph nodes (Robert-Gangneux and Dardé, 2012). However, in the early days of the AIDS pandemic, toxoplasmosis encephalitis was a defining disease in *T. gondii*-seropositive HIV-infected patients with a CD4-T cell count below 100/cm^3 (Luft and Remington, 1992). Other immunocompromised individuals, e.g. transplant recipients, are also at risk. Another vulnerable group where an infection can have profound effects are unborn children of seronegative mothers. In the absence of a maternally acquired immune response against the parasite, the acute stage of *T. gondii* can rapidly disseminate and cross the placenta, thereby also infecting the fetus and causing congenital toxoplasmosis (CT) (Dubey et al., 2021; Megli and Coyne, 2022; Milne et al., 2023). Depending on the trimester when infection occurs, it can result in severe pathologies like hydrocephalus, intracerebral calcifications, choroid plexus cysts or ocular disease. In a substantial number of cases retinochoroiditis may manifest only later in childhood, although its discrimination from a more recent infection is not easy (Garweg et al., 2022).

As a consequence of the high seroprevalence in many European countries, toxoplasmosis is regarded to be responsible for 20% of the human disease burden caused by food-borne infections in Europe (Havelaar et al., 2015). When disability-adjusted life years (DALY) per case are considered, CT is at a similar level as hepatitis B in Europe, reflecting the high individual burden despite low numbers of cases (Cassini et al., 2018). It is therefore important to have knowledge of the past and current incidence rates of *T. gondii* infection of a country's human population and follow them over time, in order to obtain reliable data that can then serve as a basis for risk assessment, public health education and possibly political decisions.

A more medically oriented description of toxoplasmosis in Germany has been previously published (Pleyer et al., 2019). In this article I will focus on three points: (i) past and current epidemiological situation, (ii) toxoplasmosis disease burden and costs for the society, and (iii) how large-scale serodiagnostics can be used to monitor these aspects in the future. The latter is the basis for the first, and consequently the accuracy, reliability and ease-of-use of serodiagnostic tests directly translates into more robust epidemiological data. Since the historical development of these points in Germany has been barely addressed in the past, they will also be illuminated by some scattered or not easy to find data.

2. *T. gondii* seroprevalences in divided Germany and after unification

Only very few nationwide *T. gondii* seroprevalence studies have been reported that are based on representative national cohorts (Table 1) rather than pregnant women only (as it is the case e.g. for studies from France and Austria) or opportunistic sampling (e.g. blood donors). Having an overall picture of a population is important since seroprevalence is age-dependent and, as reported in some studies, the susceptibility to *T. gondii* infection ('attack rate') might also differ between men and women (Bellali et al., 2013; Gay et al., 2021). Moreover, large geographical differences within a single country have been observed and depend on a variety of socio-cultural and -economic variables, as well as environmental factors important for parasite occurrence and transmission. Serological snapshots on subpopulations will therefore only provide part of the overall picture.

After World War II, the separation for 40 years of West Germany (former Federal Republic of Germany, FRG) and East Germany (former German Democratic Republic, GDR) resulted in two public health systems that differed in many aspects. It has been called by some "a natural experiment in history" (Light, 1985), referring to the common roots of its people (cultural, social, genetic and geographic) that became then exposed to different political systems and factors that affected their health to different extents (McKee et al., 1996; Reintjes et al., 2001). Notably, however, in 1989 the annual meat consumption, a known risk factor for infection by *T. gondii* (discussed below), was even slightly higher in the GDR compared to the FRG (Frei et al., 2011). After unification, it was closely followed how the public health situation developed and changed over the last three decades (Atzpodien et al., 2009; Lampert et al., 2019; Prütz et al., 2014). In 2009, most of the 20 most frequent notifiable infectious diseases (which did not include toxoplasmosis) still had a higher incidence in East Germany than in the West (Atzpodien et al., 2009).

When it was decided ten years ago to set up the first nationwide serosurvey for *T. gondii* at the RKI, the available data of the previous decades provided no clear picture of the seroprevalence in Germany. Data were scattered and locally restricted, were highly biased towards pregnant women and also performed with different seroassays, limiting their comparability (Table S1). Nevertheless, they suggested a higher seroprevalence in the former GDR as well as East Germany vs. the former FRG as well as West Germany.

Using more than 6600 sera from the population-based German representative health interview and examination survey of adults

Table 1
Basic data of nationwide serological surveys for anti-*T. gondii* antibodies.

Country	Year (s)	Seropositivity (M /F) in %[a]	Cohort (# test persons)	Age range	Serological assay / *T. gondii* antigen	Reference
Germany	2008–11	54.9	DEGS1 (6564)	18–79	ELFA / lysate	(Wilking et al., 2016)
	2014–17	6.5	KiGGS 2 (1455)	3–17	ELFA / lysate	(Giese et al., 2023)
The Netherlands	1996–97	40.5	PIENTER-1 (7521)	0–79	ELISA / lysate	(Kortbeek et al., 2004)
	2006–07	26.0	PIENTER-2 (7030)	0–79	ELISA / lysate	(Hofhuis et al., 2011)
	2016–17	29.9	PIENTER-3 (5875)	0–89	ELISA / lysate	(van den Berg et al., 2023)
USA	1988–1994	16.0	NHANES III (11,132)	12–49	ELISA / lysate	(Jones et al., 2003)
	1999–2000	15.8	NHANES (4234)	12–49	ELISA / lysate	
	2009–10	13.2	NHANES (7070)	6–70 +	ELISA / lysate	(Jones et al., 2018)
	2011–14	11.1	NHANES (13,507)	6–70 +	ELISA / lysate	(Jones et al., 2018)
UK[b]	2006–10	28	UK Biobank (9695)	40–70	BBMA / SAG1, SAG2A	(Mentzer et al., 2022)
Mexico[b]	2000	60.1	NHNS-2000 (3599)	0- > 64	In-house ELISA / lysate	(Caballero-Ortega et al., 2012)
	2006	62.6	NHNS-2006 (2916)	0- > 64	In-house ELISA / lysate	
France[b]	1997–98	65.6	2992	0–80	ELISA / lysate	(Guigue et al., 2018)
	2006–07	58.4	2429	0–80	ELISA / lysate	
	2012–13	54.7	2460	0–80	ELISA / lysate	
Portugal[b]	1979–80	47	PNSS (1675)	1- ≥ 46	ELISA / lysate	(Gargaté et al., 2016)
	2002–03	36	PNSS (1657)	1- ≥ 46	ELISA / lysate	
	2013	22	PNSS (1440)	1- ≥ 46	ELISA / lysate	

[a] unadjusted, both sexes
[b] opportunistic sampling and/or not fulfilling strict representativeness, but large datasets

(DEGS1) from 2008 to 2011 (Scheidt-Nave et al., 2012) and a commercial enzyme-immunoassay, half of the tested sera were shown to contain anti-*T. gondii* IgG (Wilking et al., 2016). There was an almost linear increase in seroprevalence with age (Fig. 1A), similar to what was found in other countries. These data indicate that adult Germans have one of the highest prevalences, at least in Europe. They also suggest that a constant exposure to *T. gondii* exists, explaining the linear increase in prevalence even in the old age groups.

In addition, using the same methodology 1453 sera from female participants (age 3–17) of the KiGGS 2 (German Health Interview and Examination Survey for Children and Adolescents wave 2) study cohort from 2014 to 2017 (Lampert et al., 2018) were analyzed recently, with an overall seropositivity of 6.3% (Giese et al., 2023).

While these two studies are the first published nationwide datasets for Germany, preliminary analyses of a previously conducted survey in 1998 (BGS98; Thefeld et al., 1999) with a similar representative sample size but using a different assay format, indicated that ca. 58% of the sera from adults were seropositive for *T. gondii* (RKI; unpublished data). Taken at face value, it would suggest a trend towards lower infection rates within a decade, which is in line with other European countries like France, Portugal, and USA, but which indicate higher reduction rates (Table 1).

Interestingly, the recently published third Dutch cross-sectional national study conducted in 2016/17 (PIENTER-3) reported surprising results (van den Berg et al., 2023). While the seroprevalence in pregnant women showed a constant decline from 1995 (54%) to 2016 (31%) in France (Robinson et al., 2021), in the Netherlands it stayed nearly constant between 2006/07 (18.5%) and 2016/17 (17.5%) (Table 1). In fact, for the whole Dutch population (age 0–79) this value even increased from 2006/07 by almost 4 %, to 29.9% in 2016/17. The reasons for this are unclear, but possible explanations and what it could mean for the German situation are discussed below.

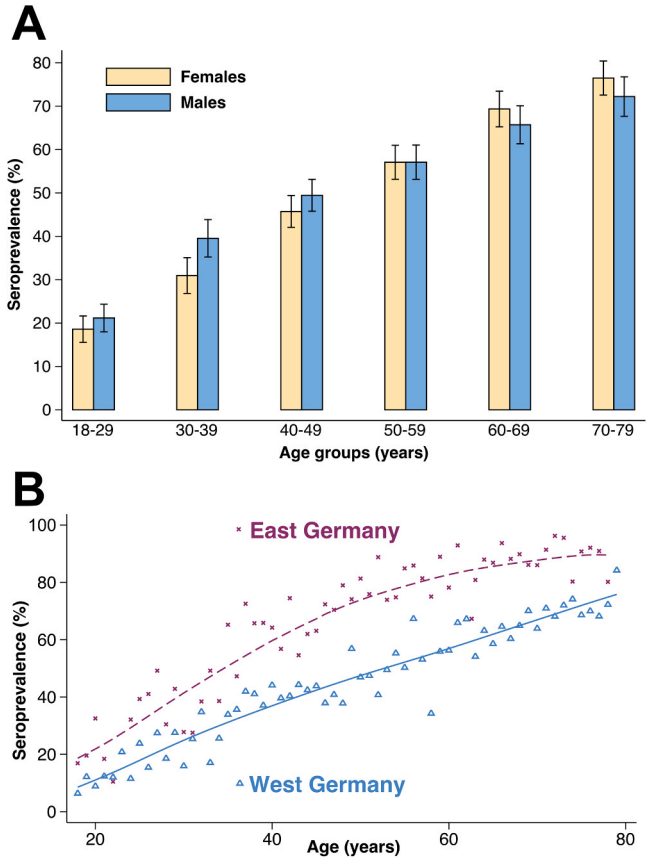

Fig. 1. *T. gondii* seroprevalence data from DEGS1 study. **A** Seroprevalence of distinct age groups, indicating its near-linear increase by age (about 1% per year of age). **B** Same data as in A, but sexes combined and separated by East and West Germany. Raw data are from (Wilking et al., 2016).

3. Risk factors for *T. gondii* infection and how they differ within Germany

One of the most striking outcomes of the DEGS1 seroprevalence study was the observation of a substantially higher percentage of anti-*T. gondii* IgG-positive individuals in the Eastern compared to the Western federal states of Germany, particularly in the age groups > 40, where it is more than 20% higher (Fig. 1B). This and the observed nationwide higher seroprevalence in males (Fig. 1A; 1.76-times higher in multivariable analysis; for details see Wilking et al., 2016) lead to the hypothesis that the consumption of raw minced meat (beef and pork), known in Germany as “Hackepeter” or “Mett”, is responsible for both findings. Minced pork is more frequently consumed in East compared to West Germany (Bremer et al., 2005; Rosner et al., 2012). Moreover, male Germans ate about twice as much meat and meat products than females (Heuer et al., 2015; Mensink and Beitz, 2004), and this was more pronounced in East Germany, where overweight is also higher (Max-Rubner-Institut, 2008). This is also in line with our data indicating that overweight and obese adults had an increased rate of seropositivity (Wilking et al., 2016). Several studies indicate that higher meat consumption is associated with increased body weight (Vergnaud et al., 2010; Wang and Beydoun, 2009; You and Henneberg, 2016), which in turn could translate into a higher chance to ingest contaminated meat, in particular where local food habits increase this risk. In contrast, vegetarians had a lower chance for seropositivity (Wilking et al., 2016). Taken together, it suggests that in Germany the main driver for *T. gondii* seropositivity is via the consumption of raw or undercooked meat. This risk factor has been observed in various other studies (reviewed in Almeria and Dubey, 2021; Ducrocq et al., 2021; Thebault et al., 2021).

Overall meat consumption in Germany is declining (Koch et al., 2021), especially pork, while this seems not to be the case for "raw sausages", which include cured meats, but also Mett sausages and the like (Fig. 2). A recent non-representative consumer survey (n = 1055; aged >17 years) suggested that 67% of males and 55% of females in Germany are at least occasionally eating raw minced pork (YouGov, 2018). These data can be compared with the situation in the Netherlands, where pork consumption is much lower but has remained almost constant over the last 15 years (Fig. 2). Yet, this led to a slight increase in seropositivity (see above), and meat consumption was found to be a risk factor, with eating raw pork tending to have a higher risk for seropositivity (van den Berg et al., 2023). It has been estimated that meat from a single pig can end up in 300–400 consumers (Fehlhaber, 2001). Thus, reducing its consumption either by eating less or even vegetarian could be beneficial, leading to a measurable decline of primary infections in the coming years.

Our findings from the DEGS1 study that vegetarians were significantly less seropositive (odds ratio 0.62 (0.42–0.99 CI)) support this hope. In this survey, the percentage of adult Germans following a vegetarian diet was 4.3%, with 6.1% of women and 2.5% of men (Mensink et al., 2016). Recent consumer surveys indicate that the number of vegetarians has increased from 5.3 million (ca. 6.4%) in 2015, to 8.1 million (9.5%) in 2023 (Institut für Demoskopie Allensbach, 2023). Notably, pigs from organic farms are known to have higher prevalences compared to animals raised under conventional pig farming conditions (e.g. indoors; Fig. 2) (Belluco et al., 2018; Dámek et al., 2023), presumably due to access to infected rodents and/or soil contaminated with oocyst-containing cat feces. Although the market share of organic meat has doubled between 2018 and 2021, this was still only 4% of the total meat market in Germany (Bundesinformationszentrum Landwirtschaft, 2022). It is difficult to predict what if any effect this will have on the overall seroprevalence (Milne et al., 2023).

Another known potential risk factor for infection is the presence of

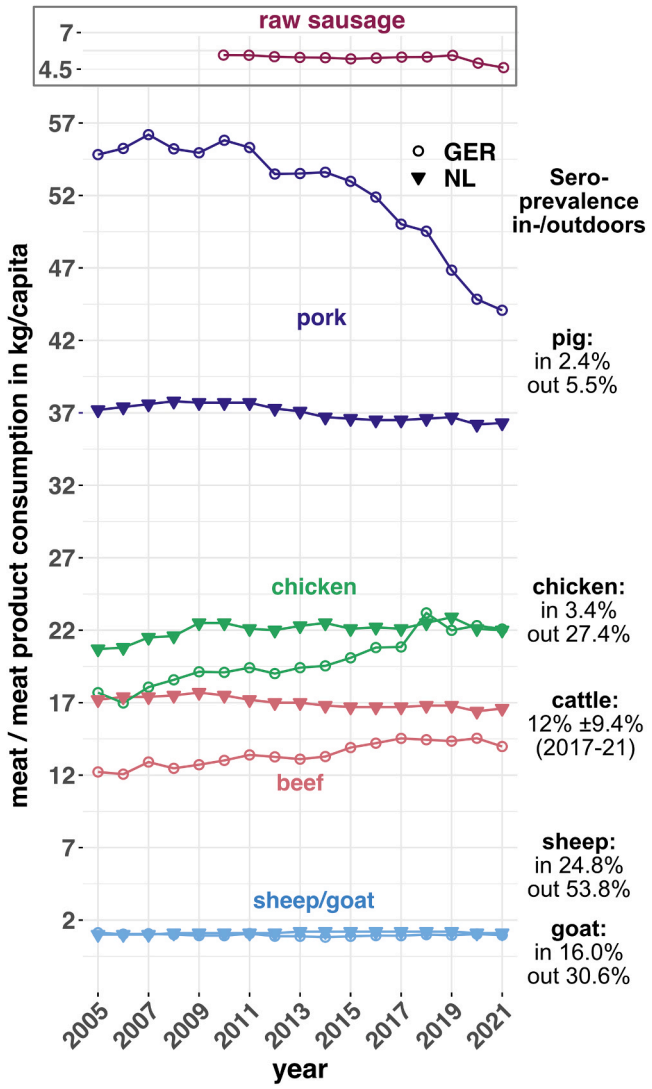

Fig. 2. Consumption of major types of meat in Germany in comparison with the Netherlands between 2005 and 2021. Data on raw sausage consumption in GER is shown as a proxy for raw meat for which no data are available. The seroprevalence of the respective animal species in both countries, differentiated between indoor (in) and outdoor (out) farming, is indicated (Dámek et al., 2023). For cattle, no modeled data are available since the presence of antibodies does not give an indication of the presence of parasites in this species (Blaga et al., 2019; Opsteegh et al., 2019). Nevertheless, to provide some rough orientation, the mean ± SD of monitoring data on *T. gondii* in cattle submitted to EFSA in 2017–21 are provided (European Food Safety Authority, 2022). Consumption is based on data from (Dagevos et al., 2022) for NL, and data and calculations for GER from (Bundesanstalt für Landwirtschaft und Ernährung, 2022) (Bundesverband Deutscher Wurst-& Schinkenproduzenten, 2022; Deutscher Fleischer-Verband, 2022).

one or more cats in the household, as found in the DEGS1 serosurvey (Wilking et al., 2016) and also by others (de Wit et al., 2019; Hofhuis et al., 2011; Jones et al., 2009; Kortbeek et al., 2004). However, this correlation was not always found in other studies (Fromont et al., 2009; van den Berg et al., 2023). This can be due to a number of reasons, including different prevalences of infected cats or multiple oocyst sheddings (Zhu et al., 2023), as well as more or less careful handling of cat litter or contact with it (Dubey et al., 2011).

Undoubtedly, oocyst shedding by cats leads to environmental contamination of water and soil, and a calculated theoretical number of 300 oocysts per m^2 per year (Table S2) is just meant to illustrate the potential risk in Germany with its currently more than 15 million cats in 2022. However, this number is consistent with other estimates, and in particular in urban areas public places like playgrounds could pose an increased risk (Torrey and Yolken, 2013). Increased heavy rainfall events due to climate change can also lead to contamination by run-off water of otherwise "cat-free" places, not only in coastal but also in urban areas (Schreiber et al., 2019; VanWormer et al., 2016). Other scenarios, such as contamination of recreational areas after flooding or sewage spill-overs, as has been reported for a *Cryptosporidium hominis* outbreak in Halle (Saale) ten years ago (Gertler et al., 2015), are also possible. However, because acute cases of toxoplasmosis are usually clinically mild and therefore frequently overlooked, such data are lacking for *T. gondii*.

A major general problem with these analyses is that risk factors are mostly studied in retrospect and based on IgG seropositivity, providing no information of when the infection occurred. Thus, there is a lack of knowledge about how this is related to 'risky behavior' that dates back weeks or months. A study on risk factors for acute toxoplasmosis, based on data from regional medical microbiology laboratories and questionnaires, has been recently reported from the Netherlands (Friesema et al., 2023), an approach that should also be envisaged for Germany.

Collectively, it is currently very hard to make any predictions regarding *T. gondii*'s seropositivity trend and its connected risk factors. Consequently, public awareness for those risks is important and available (Pleyer et al., 2019). However, more has to be done, since a recent study reported that 48% of Germans older than 16 years (n = 1008) had never heard of *T. gondii* or toxoplasmosis (Henke et al., 2020). 32.8% had at least heard of it, but only 18.8% knew of preventive measures for infection.

4. Burden of toxoplasmosis in Germany - then and now

In the FRG, toxoplasmosis was a notifiable disease from 1962 to 1979 (Janitschke, 1996). Any case of illness or death due to *T. gondii* had to be reported (even by the head of the family (!), Bundestag BRD, 1961), but from 1980 onwards only congenital toxoplasmosis was a notifiable disease (Fig. 3). In contrast, in the GDR data were collected from 1955 up to 1989 (Pöhn and Rasch, 1994) at the central and district levels from 21 laboratories as part of annual routine serosurveillance studies (Glathe and Rasch, 1992; Pöhn and Rasch, 1994). Serologic testing of pregnant women was performed before the 13th week of pregnancy, then between the 30th and 32nd week, and finally at delivery. Chemotherapy was started when the titer in IFA was above a certain threshold, although available drug preparations were reported to be sub-optimal (Janitschke, 1996). Whether the latter had any influence on congenital mortality (Fig. 3) is not known.

Mortality of general toxoplasmosis and congenital disease declined over the years in both parts of Germany, whereas morbidity apparently rose strikingly in the GDR in the 1980 s. However, this has been explained by the improved detection of primary infections in pregnant women due to increased routine serological testing, and were included in the statistics, even when no clinical signs had been reported (Pöhn and Rasch, 1994). Another likely contributing factor is that the assays used for serological testing with their inherent variability were replaced by more standardized and sensitive commercial ELISA-based methods, in particular in the GDR (Janitschke, 1996; Ockert, 1992) (Table S1).

How is the current situation in Germany? Although healthcare claims based on the 10th revision of the International Statistical Classification of Diseases (ICD-10) must be viewed with some caution, as their accuracy can vary and they are primarily used for financial reimbursement rather than disease surveillance or epidemiological research, they can still be informative. An analysis of hospital discharge of toxoplasmosis patients, based on ICD-10 code B58 (the code for toxoplasmosis), from 2000 to 2016 provided an indication for a higher disease burden in North-Eastern Germany (Pleyer et al., 2019), and this is still true when the latest data are incorporated (Fig. 4A). It is consistent with the higher seroprevalence found in these regions of Germany (Wilking

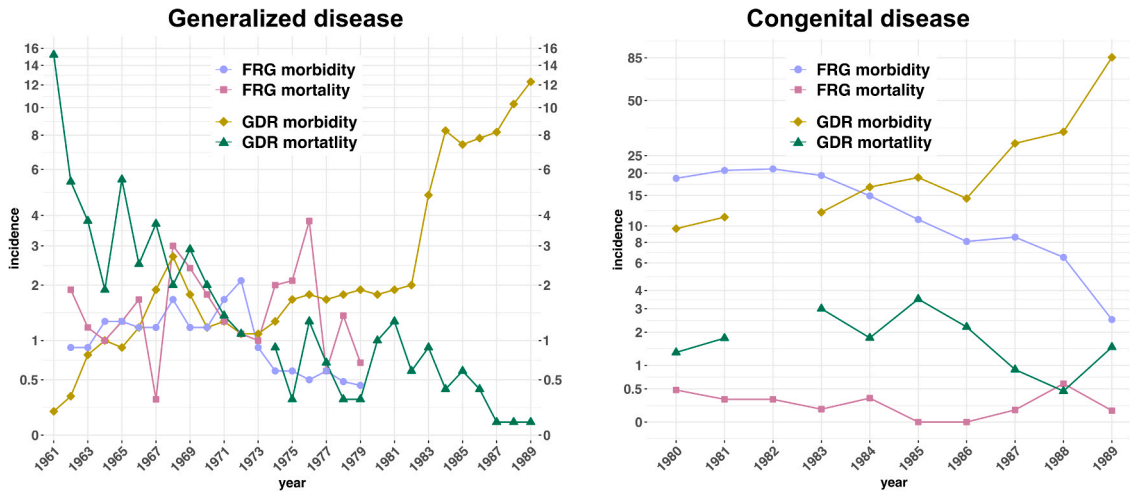

Fig. 3. Course of morbidity and mortality data of toxoplasmosis in both parts of Germany over three decades (1961–1989). Left: generalized toxoplasmosis; right: congenital toxoplasmosis. Incidence is given per 10^5 inhabitants. The y-axis is drawn as log2. Raw data are from Epidemiologisches Zentrum der Staatlichen Hygieneinspektion, 1988; Pöhn and Rasch, 1994).

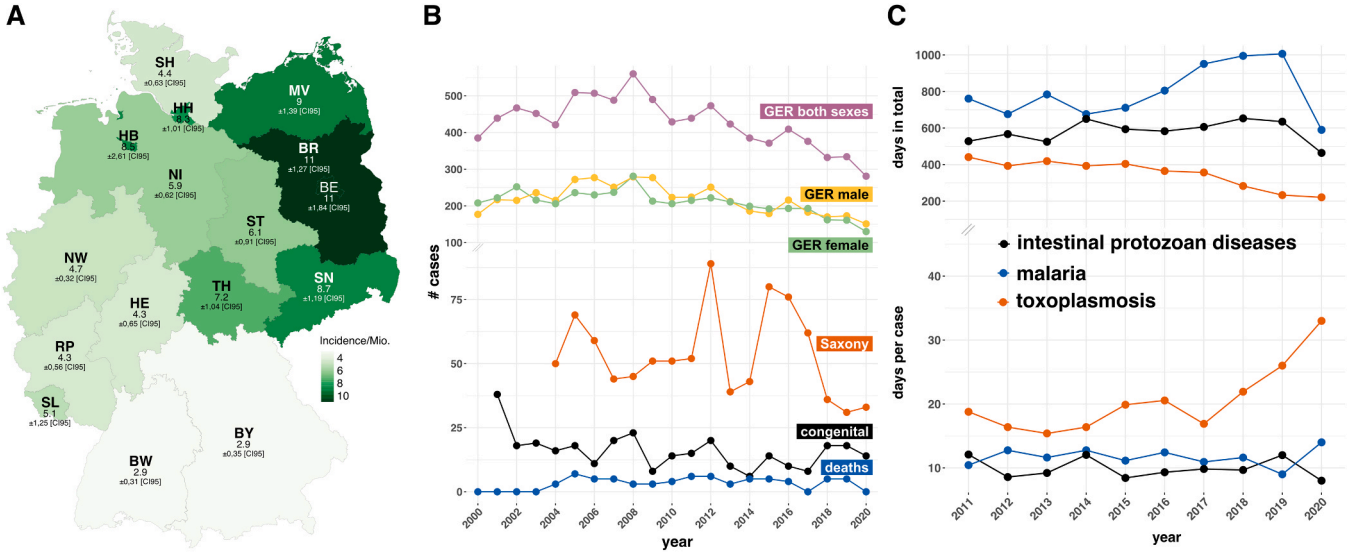

Fig. 4. Numeric indicators of annual toxoplasmosis cases in Germany. **A** Cumulative data from the number of annual discharged hospitalized patients (inhabitants of the respective state), based on ICD-10 code B58, from 2000 to 2020, provided as incidence per 10^6 inhabitants (mean ± 95% confidence interval, CI). BE, Berlin; BR, Brandenburg; BW, Baden–Württemberg; BY, Bavaria; HB, Bremen; HE, Hesse; HH, Hamburg; MV, Mecklenburg–West Pomerania; NI, Lower Saxony; NW, North Rhine–Westphalia; RP, Rhineland–Palatinate; SH, Schleswig–Holstein; SL, Saarland; SN, Saxony; ST, Saxony–Anhalt; TH, Thuringia. Raw data are from (Statistisches Bundesamt GBE, 2022). **B** Number of annual discharged hospitalized patients, based on ICD-10 code B58 from 2000 to 2020 (Statistisches Bundesamt GBE, 2022). In the upper part, sex-specific as well as their combined numbers are given. At the bottom, fatal outcomes are shown. In addition, annual cases of Saxony, the only federal state where also general toxoplasmosis is notifiable, are shown (Statistisches Landesamt Sachsen, 2022). Congenital cases reported to the RKI are also provided (
Source: SurvStat@RKI 2.0). **C** Absence from work (both sexes) as a result of sick days due to toxoplasmosis in comparison to malaria or other intestinal protozoa. The top part shows the total days of all cases per year, while the bottom part shows the days per case. Raw data are from the "Results of the Statutory Health Insurance Disease Type Statistics", reporting the data of compulsory members other than pensioners (Bundesgesundheitsministerium, 2022).

et al., 2016). Observing these data over the last two decades suggests a trend towards lower numbers during the last ten years (Fig. 4B). This is not obvious in the number of CT cases reported to the RKI and the fatal cases of toxoplasmosis reported by hospital discharge data, although the absolute numbers in both cases are very small, precluding robust statistical conclusions.

Interestingly, looking at the statistics of 'absence from work' due to sick days caused by toxoplasmosis, a decline in the overall days over the last ten years is also observed, whereas the days per case increased substantially since 2017 (Fig. 4C). The reasons for this are currently unknown, but they illustrate the fact that despite the lower number of cases compared to other protozoan diseases, the loss of work and thus costs for the society are higher than for instance for malaria.

To gain further insight into cases of toxoplasmosis requiring treatment, a study based on healthcare claims data in Germany was recently performed (Krings et al., 2021). It covered the years 2011–2016 and included data from 4.8 to 5.2 million insured persons. An average of 8061 annual toxoplasmosis patients was determined, of which 36% could be assigned to a specific disease condition. Of those, most were OT cases, accounting for 1601 cases per year. This is in line with an estimated 1300 to 1711 annual cases, calculated from the reported incidence values of uveitis (between 38 and 50 cases /100,000 patients;

(Barisani-Asenbauer et al., 2012; Deutsche Ophthalmologische Gesellschaft, 2010)) and an estimated 4.2% of those being due to OT (Jakob et al., 2009; Maenz et al., 2014).

With regard to CT, for the years 2011–2016, 43–116 cases were found, compared to an estimated 345 children in the previous study (Wilking et al., 2016) (based on the assumption that 27% of infected neonates develop symptoms of CT; Dunn et al., 1999). The differences in the incidences can be explained by procedural differences (Krings et al., 2021) but confirm the previously expressed concerns that the number of annual cases reported to the RKI, being constantly below 25 (Fig. 4B), is due to vast underreporting. The exact reasons for this are unclear but require further attention. Overall, the incidence of toxoplasmosis seemed to decline in the study period, in line with other data discussed before. However, public and physician awareness should be improved to consolidate this trend (Pleyer et al., 2019). The flattening trend in the Netherlands could be a cause for concern.

Besides greater efforts to raise awareness, expanding and harnessing the potential of serological diagnostic tests could contribute to investigate cause-effect relationships between temporal changes in known and emerging risk factors and incidence of *T. gondii* infections.

5. History of *T. gondii* serodiagnosis in a nutshell

Only accurate, reliable, easy-to-use and affordable serodiagnostic tests allow the generation of robust epidemiological data. How this can influence morbidity curves has been discussed above (Fig. 3). Fortunately, serological tests for *T. gondii* have been constantly improved over time (Fig. 5). Most were adapted from assays previously developed in other contexts and fields (Dubey and Beattie, 1988; Ybañez et al., 2020). However, a unique assay is the Sabin-Feldman dye test (SFDT), which is still considered by many the gold standard test, despite its first description dating back to 1948 (Sabin and Feldman, 1948), due to its specificity and sensitivity (Reiter-Owona et al., 1999). It relies on the inability of methylene blue uptake by live *T. gondii* tachyzoites due to their lysis in the presence of either *T. gondii*-specific IgM, IgG or IgA antibodies. It requires complement as so-called 'accessory factor' (Suzuki and Tsunematsu, 1971). The simultaneous indirect 'detection' of these antibody classes allows a diagnosis of presumably acute (IgM, IgA) as well as more chronic infection (IgG). However, the test requires highly skilled and experienced personnel as well as live parasites and is thus used only by a few specialized laboratories any more. Since detection of cytolysis is the underlying principle of the assay, an enzyme-release assay based on transgenic parasites expressing bacterial β-galactosidase as a reporter for cell lysis has been described (Dando et al., 2001; Seeber, 2000) but did not find widespread use.

Several of the other early tests are still in use (e.g. direct agglutination test (DAT) and latex agglutination test (LAT)), in particular for testing animal sera (Dubey, 2021). However, most assays used in clinical settings for diagnosing human *T. gondii* infection, including confirmatory tests to discriminate chronic from acute infection via antibody avidity, are now largely based on enzyme-immunoassays (ELISA, or ELFA (enzyme-linked fluorescent assay)). They are available from many vendors and have reached a high degree of standardization, with excellent results regarding specificity, sensitivity and ease of use (Robert-Gangneux and Guegan, 2021). In the USA, very good results have recently been reported with a commercially available lateral flow assay (LFA) as a point-of-care test, intended in particular for pregnant women with sub-optimal or no health insurance (Abraham et al., 2023; Mahinc et al., 2017). The aim is to prevent congenital infections by easy and affordable access to such a test. Whether it is an option for Germany remains to be evaluated, given the very different prevalences in both countries (Table 1) and the fact that this test requires a high negative predictive value in order to be useful.

Initially, in all assays either whole tachyzoites or lysates thereof were (and still are) used as antigen, while most tests currently under development by research labs are based on recombinant *T. gondii* proteins (or fragments thereof) (Holec-Gasior, 2013). Besides the obvious advantages of unlimited amounts of antigens without parasite cultivation, this approach also allows the incorporation of antigens from different infectious stages, i.e., bradyzoites and oocysts/sporozoites.

6. Development and potential of large-scale assays for future serosurveys

While *T. gondii* serology for small- to medium-scale projects is logistically not problematic with ELISA-based methods, there is currently no commercial test available that would be optimal for the screening of thousands of sera, as it is required for representative population-based studies. The introduction of the fluorescent bead-based multiplex assay (BBMA) platform in the mid-1990 s (Luminex xMAP technology), which allows multiplexed immunoassays in a microplate format (Graham et al., 2019), has greatly changed the way such studies can be performed. Its principle is depicted in Fig. 6A-C. Its main advantage for serology lies in the fact that dozens of different antigens can be incorporated into a single experiment using only one serum sample. A fluorescence reader with two channels can distinguish the beads (bearing different antigens) according to their unique intrinsic fluorescence and simultaneously detect and quantify the intensity of the fluorescent label on the secondary antibody. The antigens can derive from the same or different pathogens, thus allowing to increase the specificity (in case single antigens would not suffice) and/or to simultaneously monitor immune responses directed against several distinct organisms. The methodology is thus very economic, both in terms of labour and amount of serum required.

The interest in such BBMA-based, large-scale surveys has increased in recent years, not the least due to the COVID-19 pandemic (Arnold et al., 2018; Arnold et al., 2017; Haselbeck et al., 2022; Metcalf et al., 2016). However, no commercial BBMA for *T. gondii* is currently available.

Given the RKI's interest in representative population-based surveys,

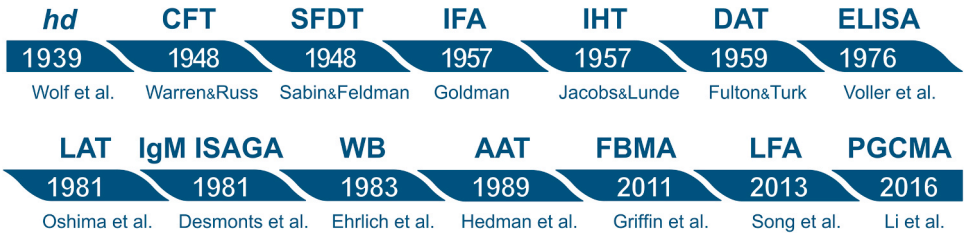

Fig. 5. Time line of first descriptions of *T. gondii*-specific serological assays of human sera. Abbreviations: hd, human disease by *T. gondii* first described by (Wolf et al., 1939); CFT, complement fixation test (Warren and Russ, 1948); SFDT, Sabin-Feldman dye test (Sabin and Feldman, 1948); IFA, immuno-fluorescent assay (Goldman, 1957); IHT, indirect hemagglutination test (Jacobs and Lunde, 1957); DAT, direct agglutination test (Fulton and Turk, 1959); ELISA, enzyme-linked immunosorbent assay (Voller et al., 1976); LAT, latex agglutination test (Ohshima et al., 1981); IgM ISAGA, IgM immunosorbent agglutination assay (Desmonts et al., 1981); WB, Western blot (Erlich et al., 1983); AAT, antibody avidity test (Hedman et al., 1989); FBMA, fluorescent beads multiplex assay (Griffin et al., 2011); LFA, lateral flow assay (Song et al., 2013); PGCMA, plasmonic gold chip multiplex assay (Li et al., 2016). For review see (Dubey, 2021; Ybañez et al., 2020).

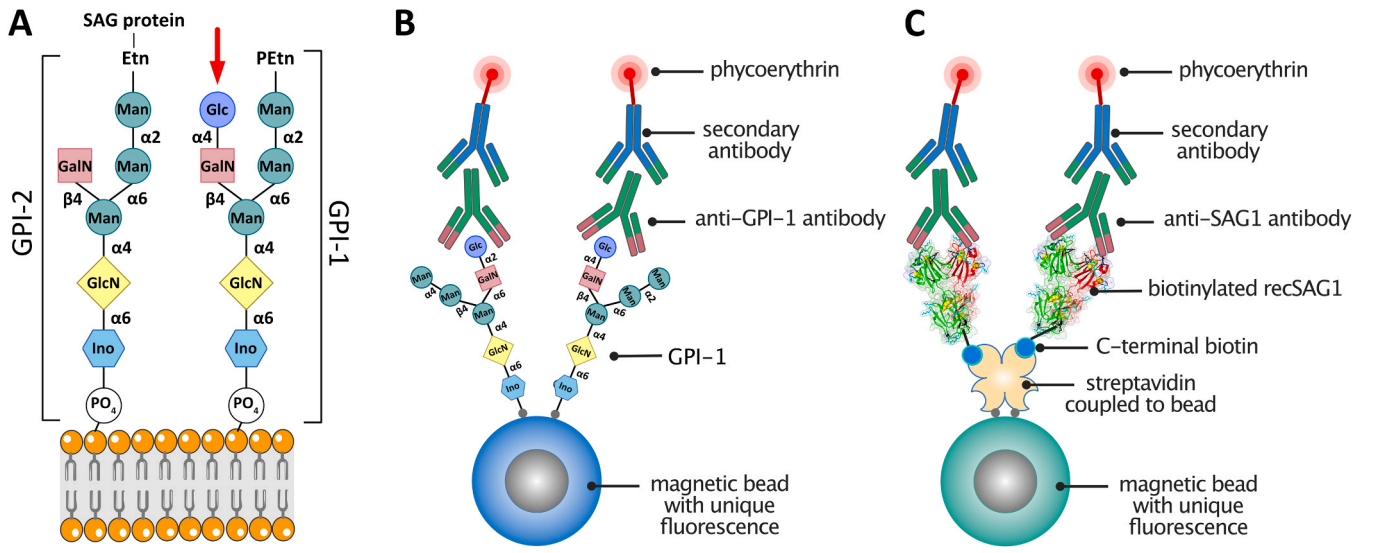

Fig. 6. Concept and details of BBMA for *T. gondii,* based on SAGs and GPI-1. **A** Simplified scheme of GPI-anchored SAG proteins and protein-free GPI-1 in the membrane. Etn, ethanolamine; Man, mannose; GalN, galactosamine; GlcN, glucosamine; Ino, inositol. Arrow points to the unique glucose. **B, C** Structure and formation of the BBMA components after addition of serum and detection antibody, with either GPI-1 (B) or $SAG1_{bio}$ as antigen (C).

a BBMA was established that contained two surface proteins of *T. gondii*, surface antigen 1 (SAG1; also called p30) and surface antigen 2 A (SAG2A; p22) (Klein et al., 2020). These immunodominant and parasite-specific antigens, in particular SAG1, have been used successfully in *T. gondii* serology for years (Wang and Yin, 2013). The test design is fundamentally different from previous BBMA in that it contains both recombinant proteins, expressed in a way that a C-terminal biotin residue is added during protein synthesis in the bacterial cell, resulting in biotinylated proteins ($SAG1_{bio}$/$SAG2A_{bio}$). Accordingly, they can bind to bead-coupled tetrameric streptavidin (Fig. 6C). This results in a defined and oriented tight coupling of the proteins to the beads, whereas the usual chemical crosslinking via lysine residues is non-selective and could potentially obscure important epitopes (Klein et al., 2020). Since SAG1 and SAG2A are bound to the parasite's plasma membrane via a C-terminal GPI anchor (GPI-2 in Fig. 6A), the biotinylated protein approach results in a similar presentation of its dominant N-terminal conformational epitope to the surrounding environment (Graille et al., 2005). In this respect, it also differs from ELISA-based assays where attachment to the plastic is random and less tight. Comparing this BBMA with those from the literature indicates that it has many advantages, including high sensitivity and specificity, even when $SAG1_{bio}$ is used alone, and ease of protein purification and coupling to the magnetic beads (Klein et al., 2020).

The GPI-anchor which attaches SAG1 to the membrane also exists as a protein-free form in the parasite, but with an important modification: it contains an additional glucose in the side chain of the glycan structure (GPI-1; Fig. 6A). GPI-1 itself was found to be of high diagnostic value in earlier studies, being able to detect also early IgM responses in infected humans (Götze et al., 2014; Striepen et al., 1997). Interestingly, the glucose modification is essential for antibody recognition and specificity, as shown by chemically synthesized GPI-1 glycans and derivatives (Götze et al., 2014). It was therefore of interest to see whether the GPI-1 glycan, attached to magnetic beads in an oriented way by a specific linker chemistry, would also be compatible with the BBMA format (Garg et al., 2019). Indeed, anti-*T. gondii* IgG and IgM antibodies reliably bound to GPI-1, whereas $SAG1_{bio}$ performed well only in detecting IgG antibodies. Although further studies are required to substantiate these first results, GPI-1 is one of the few antigens known that allows such an early detection of a *T. gondii* infection. It could supplement the $SAG1_{bio}$-based BBMA when used in a recently introduced dual-reporter flow analyzer instrument with three channels. This enables the detection of two different fluorophores, e.g. attached to anti-IgG and anti-IgM secondary antibodies, in the same assay (Cameron et al., 2022). For large serosurveys, it would allow the determination of the recent infection rate (estimated to be 1–3%) in a whole population, at little additional cost. Moreover, this example illustrates that different immobilization strategies, required by different antigens for best performance, can be combined in a single platform (Garg et al., 2019), which would be hard to achieve with an ELISA-based assay.

It is estimated that more than 40% of human infections could be due to ingestion of oocysts (Cook et al., 2000; Jones et al., 2009). Therefore, there is an urgent need for robust data on the contribution of oocysts to infection (Álvarez García et al., 2021). Large serosurveys could play a major role for this, once reliable antigens with source-attributing potential, i.e., being able to discriminate between oocyst- versus tissue cyst-derived infections, have been identified. While some *T. gondii* antigens have been claimed in the past to fulfill this role, a recent study using more stringent source attribution criteria has shown that this goal has yet to be achieved (López-Ureña et al., 2023). Nevertheless, the BBMA is perfectly suited to incorporate this kind of stage-specific antigens once they have been better defined. Moreover, in the veterinary sector, performing toxoplasmosis serology alone for screening purposes might not be attractive, but when combined with antigens of other zoonotic pathogens it could be a cost-effective and valuable tool from a One Health perspective. Notably, it was shown recently that the $SAG1_{bio}$-based BBMA can be easily adapted for chicken serology (Fabian et al., 2020).

7. Conclusions

Toxoplasmosis in Europe and also in Germany is one of the major contributors of foodborne diseases with regard to DALYs. Although low in numbers compared to other diseases, its burden is measurable, and congenital and ocular toxoplasmosis can have serious lifelong consequences for the affected. The seroprevalence was and still is high in Germany and exposure to the parasite seems to persist livelong, evidenced by the steady increase of seroprevalence with age. The main sources of infection in Germany are presumably the consumption of raw or undercooked meat from infected livestock and could be largely avoided by an informed population. However, the tradition of eating raw minced meat or sausages in Germany seems difficult to break.

Nevertheless, some data suggest that, as it is in other countries, the

number of infections are declining also in Germany, albeit slowly. It is important to follow this trend with further representative serosurveys, combined with data on diet and eating habits. Whether the increasing number of vegetarians and vegans on one side and the increasing proportion of organically produced meat (with its higher infection rates) versus the lower consumption of pork (with its decreased chance to consume infected meat) on the other side has any measurable influence on seropositivity could ideally be measured by such studies.

Of outmost importance for reliable serology data are robust and efficient assays like the BBMAs discussed. Its potential to incorporate dozens of different antigens (stage-specific or from other pathogens) and quantify two antibody classes at the same time with the same serum sample offer unique opportunities. The advances since the early days of *T. gondii* serodiagnosis are thus immense.

CRediT authorship contribution statement

Seeber Frank: Conceptualization, Formal analysis, Funding acquisition, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declarations of Competing Interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ijmm.2023.151592.

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Corrigendum

Corrigendum to "Past and present seroprevalence and disease burden estimates of *Toxoplasma gondii* infections in Germany: An appreciation of the role of serodiagnostics" [Int. J. Med. Microbiol. 313 (2023) 151592]

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It was noted that in Figure 4C, top part, there was an error in the labelling of the y-axis. It should read "cases" instead of "total days". Accordingly, the legend to Figure 4C should read "The top part shows all cases per year". This error does not affect any conclusions in the text.

The author and the Publisher regret the error that appeared in the paper.

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