



# Pathogenesis of tuberculosis: the 1930 Lübeck disaster revisited

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**The Lübeck disaster emphasises that tuberculosis disease in nearly all infants develops soon after primary infection. Failure to institute chemoprophylaxis as soon as possible post-infection exposes infants to a considerable risk of serious disease or death.** <https://bit.ly/3yj7k7C>

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## Abstract

During the 1930 Lübeck *Mycobacterium bovis* bacille Calmette–Guérin (BCG) disaster, 251 neonates received three oral BCG doses accidentally contaminated by virulent *Mycobacterium tuberculosis*; 67 (26.7%) infants died of tuberculosis. BCG reversion to pathogenicity did not occur. Detailed *post mortem* examinations clarified contested aspects of tuberculosis pathogenesis. Gastrointestinal infection was seldom “silent” and did not cause typical primary pulmonary lesions. In 15 infants, primary pulmonary foci were found but these resulted from vaccine ingestion and aspiration and were not caused by gastrointestinal infection spreading to the lungs without trace of its journey, as claimed by prominent researchers such as Calmette and von Behring. Further, among 60 infants in whom *post mortem* evaluation was completed, a “silent” gastrointestinal infection without an intestinal primary focus was found in only one. Lymphohaematogenous-disseminated tuberculosis caused death in 24/67 (35.8%) infants and tuberculous meningitis in a further 17/67 (25.4%). Gastrointestinal tuberculosis complications caused death in 26/67 (38.8%) infants. Half of the tuberculosis-attributed deaths had occurred by 3 months, 93% by 6 months and 100% by 12 months; remarkably no further deaths or tuberculosis recurrences occurred within 5 years post-vaccination/infection. These findings provide graphic confirmation that the early introduction of chemoprophylaxis in recently *M. tuberculosis*-infected young children is critical and urgent.

## Introduction

The Lübeck *Mycobacterium bovis* bacille Calmette–Guérin (BCG) tuberculosis vaccination accident (historically referred to as the “Lübeck disaster”), which unfolded during early 1930, caused death attributed to tuberculosis of over a quarter of vaccinated infants, and cast doubts over live vaccines for disease prevention, but contributed to a fundamental reappraisal of the pathogenesis of tuberculosis and a reassessment of research procedures in patients. When the tragedy’s extent became apparent, an intensive mechanism of observation, investigation and management commenced; these efforts were collated by Albert Moegling of the German Ministry of Health and the results published in 1935 [1]. Although later publications summarised these events, the anatomical-pathology findings and their relevance regarding the pathogenesis of tuberculosis and the underlying cause of the tragedy are not widely appreciated [2–4]. We reviewed this unique event from original literature sources, thereby providing a better understanding of the pathology and pathogenesis of tuberculosis, in particular gastrointestinal primary infection with *M. tuberculosis* and its consequences.



## Methods

From 7 April until 6 May 2021, a trained medical librarian performed a systematic literature search, primarily using Medline Ovid (Medline on OvidSP) and Embase with selections of keywords for different subtopics. The concepts were developed using both controlled and natural languages. MeSH terms were used, and keywords were gathered along with various synonyms. Search terms included “Bacille Calmette Guérin”, “BCG”, “BCG-itis”, “bovine”, “Calmette”, “Guérin”, “Lübeck disaster”, “Luebeck disaster”, “Lubeck disaster”, “Mycobacterium bovis”, “Mycobacterium tuberculosis”, “PPD”, “purified protein derivative”, “Robert Koch”, “strains”, “tuberculosis” and “tubercle bacillus”. The keywords were searched using the title, abstract and keyword fields within the Medline Ovid and Embase databases. For continuity, after translation, the searches were all run again in each database. Search results underwent automated and manual de-duplication within EndNote citation manager. Thereafter, two authors (C.L. and A.M.M.) manually reviewed titles to exclude literature not relevant to the topic. In addition, publications in the German, French and English literature from the authors’ existing historical collections and a further search of contemporary articles referenced in the official report [1] were included, and their references were searched for relevant additional literature.

## Background

The chief individuals involved in the genesis of the 1930 Lübeck events were George Deycke, physician and director of Lübeck General Hospital, and Ernst Altstädt, chief tuberculosis treatment physician of Lübeck Internal Medicine Services. Both had extensive experience of tuberculosis management and treatment research and were respected by colleagues and the Lübeck community.

Deycke trained as a physician and worked initially at Eppendorf Hospital in Hamburg. He assisted in establishing a medical faculty in Istanbul in 1898 and was director and chief physician of the Royal Osman Guilane Hospital from 1903 to 1907 [5]. During 1908, he was director of leprosy services in British Guyana and evaluated a leprosy treatment based on a mycobacterial fat nastin, that appeared to ameliorate immune responses in some patients [6]. Returning to Hamburg, he worked at Eppendorf Hospital until 1913 when he was appointed director of Lübeck General Hospital.

Altstädt, a student of tuberculosis researcher Hans Much, trained in Hamburg and moved to Lübeck with Deycke in 1913. Deycke and Altstädt worked closely with Much developing immunological tuberculosis treatments based on eliciting antibodies to certain *M. tuberculosis* antigens known as partigens [7, 8]. Partigen treatment of tuberculosis was used for several decades with varying results [9–11]. Partigen-related research continued following Deycke’s Lübeck appointment; a consequence of this was the presence of the *M. tuberculosis* “Kiel” strain in the Lübeck General Hospital laboratory [12].

In 1930, Albert Calmette summarised events preceding the first German BCG vaccination programme in the old Hanseatic town of Lübeck [13]. On 24 July 1929, the Lübeck Health Office, on behalf of Altstädt, requested a BCG culture from Institute Pasteur for vaccination among the socially uninsured Lübeck population. On 27 July 1929, the Institute Pasteur Vaccine Section dispatched BCG vaccine 374 to Lübeck. This strain was used in France in August 1929 to vaccinate 573 infants and also supplied to Mexico and Latvia; no adverse events were recorded. Calmette and Camille Guérin maintained the vaccine on glycerine–potato medium and used liquid Sauton’s medium when preparing the vaccine. In contrast, Deycke used solid culture media during vaccine preparations undertaken by an assistant who had worked with Deycke for 17 years preparing partigens but was not professionally qualified for laboratory work [14]. Furthermore, disregarding Calmette’s recommendations to minimise risk of contamination, the Lübeck laboratory utilised two partially separated areas; BCG cultures were incubated in the smaller area A and the Kiel strain was incubated in space B where BCG vaccine and partigens were prepared (figure 1). The incubators were not locked. There was no separate designated area for culture and vaccine reconstitution. Further, once prepared, the vaccine did not undergo animal evaluation confirming lack of virulence.

The vaccination programme was approved by the Lübeck Health Council and Medical Practitioners Council. In late February 1930, Lübeck posters advertised the programme (figure 1) and newspapers urged public support. Although initially intended for infants from a tuberculosis milieu (persons living under conditions where transmission events of *M. tuberculosis* are likely to occur, *e.g.* under crowded housing conditions), vaccination was later offered to all newborns. Following Calmette’s recommendations, the infants were to receive 10 mg of vaccine orally on three separate occasions within 10 days post-birth.

In March 1927, the German Government Health Advisory Council discussed BCG vaccination but considered the evidence insufficient to recommend BCG [15]. Nevertheless, BCG was occasionally used and several hundred children in Bleialf in Eifel, Breslau and Berlin were vaccinated [16, 17].



**FIGURE 1** Photograph of the original bacterial incubator from the Lübeck city hospital (left; courtesy of Medizinhistorisches Museum Hamburg, Germany, Mr. Henrik Essler. Photo: Mrs. Claudia Ketels, Photo- und Graphik Department, University Hospital Hamburg Eppendorf, with permission) and a poster from the Lübeck public health authorities advocating for oral bacille Calmette–Guérin vaccination in the first days of life of newborn babies (right). One passage of the text states: “This means of protection is completely harmless, it does not result in any health disorders”.

### The Kiel strain

The Kiel strain was isolated in 1927 from a 4-year-old child with hip tuberculosis cared for by Hans Opitz in the Charité Hospital, Berlin. Initially known as H29 or “Werner”, Opitz studied this mycobacterium and considered it had *M. bovis* characteristics. Both Opitz and Bruno Lange of the Robert Koch Institute thought its virulence was markedly attenuated [18]; Lange commented that “Werner” was the same organism as the Kiel strain [19] that on 29 September 1929 was forwarded from Kiel to Deycke for partigen preparation [12, 20]. It had an unusual characteristic in that it frequently stained Sauton culture media green, facilitating its later identification.

### The unfolding tragedy

The vaccination campaign began in late February 1930, but three infants were vaccinated earlier. On 12 December 1929, an infant whose mother had severe pulmonary tuberculosis and was sputum microscopy-positive for acid-fast bacilli received the first vaccine doses; it was later established that these doses were contaminated by the Kiel strain. This infant presented on 15 January 1930 with cervical lymphadenopathy. Biopsy culture revealed virulent human *M. tuberculosis*; unfortunately, it was assumed that the infant had congenitally acquired tuberculosis. Two more infants were vaccinated on 30 December 1929 and 10 February 1930.

On 17 April 1930, an infant vaccinated 33 days previously died; permission for a *post mortem* examination (PME) was refused. Another death occurred on 20 April 1930; on PME extensive respiratory tuberculosis was found with mesenteric nodal infiltration. Pulmonary tuberculosis was diagnosed as the mother had pulmonary tuberculosis. However, the death of two more vaccinated infants on 25 and 26 April 1930, both with severe abdominal tuberculosis, placed the matter beyond doubt [21]. The vaccine emulsions prepared in Lübeck were probably contaminated by virulent bacilli.

### The response to the vaccination accident

As the nature of the tragedy became apparent, live-vaccine opponents claimed reversion of BCG to virulence [22]. Simultaneously, detailed documentation of events commenced, supported by the Ministry of Internal Affairs coordinated by Moegling of the Health Ministry, Bruno Lange and Ludwig Lange from the Robert Koch Institute were responsible for microbiological aspects, and PMEs were undertaken or supervised by Paul Schürmann from Berlin.

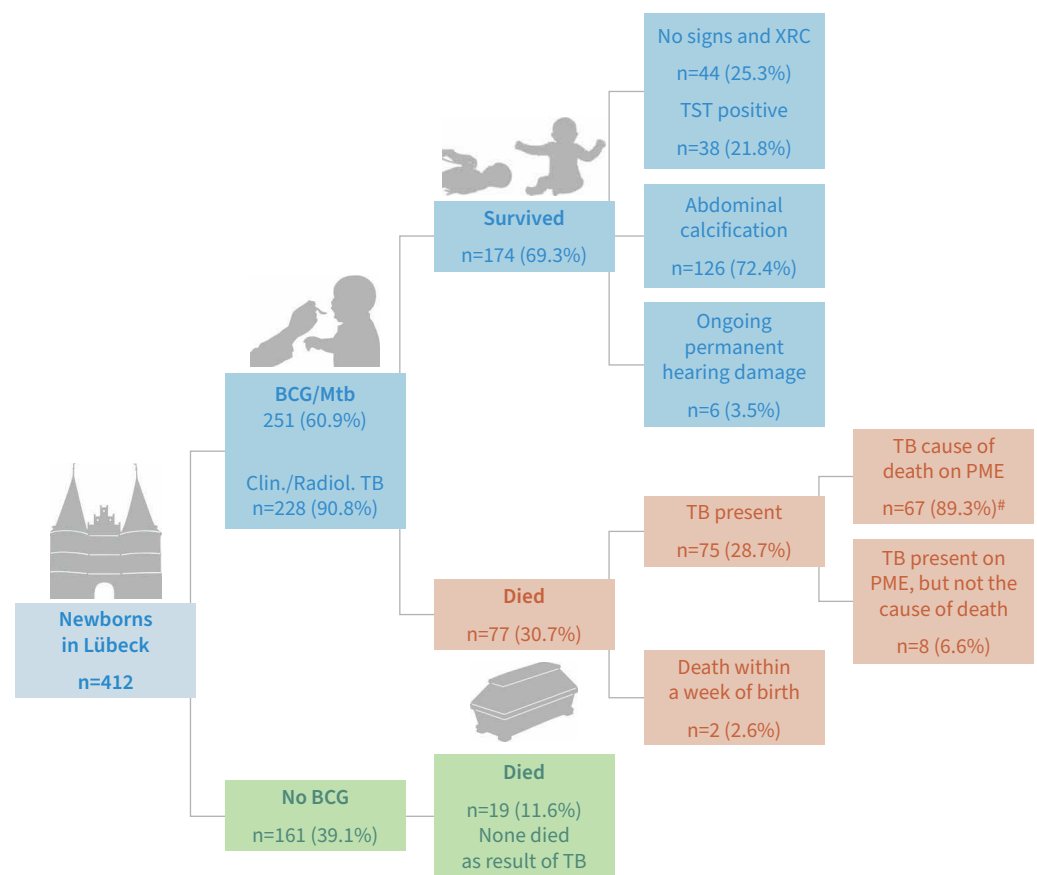
The course of events following the initiation of the BCG vaccination programme is summarised in figure 2. Of 412 infants born in Lübeck, 251 (60.9%) received BCG; 77 (30.7%) vaccinated infants died, but 10 from causes other than tuberculosis. A PME was carried out on 72 (93.5%) infants; the parents refused permission in five instances. A 2-year-old boy also inadvertently ingested vaccine while accompanying his mother and newborn brother for vaccination. He became tuberculin skin test (TST)-positive and later mesenteric calcifications were identified on abdominal radiography [23].

On learning of the vaccination accident, Calmette systematically described all means by which BCG contamination could have occurred and precautions taken in the Pasteur Institute [13]. Considerable numbers of infants were already BCG-vaccinated (in France alone 242,250) without complications or reversion to pathogenicity.

Documentation of the tragedy included recording details of the consequences of probable infection of 251 newborn infants with uncertain amounts of *M. tuberculosis*. A card system recorded every event, and the infants were regularly evaluated clinically, chest and abdominal radiographs taken, and TST sensitivity documented. Hans Kleinschmidt from Cologne supervised clinical evaluation and his assistant Mina Böcker was responsible for TST [24]. Hermann Jänasch and Gertrud Remé coordinated radiological evaluations [23].

**Vaccine contamination**

Detailed microbiological investigations, including guinea pig experiments, rejected BCG reversion to pathogenicity [12, 25]; *M. tuberculosis* “Kiel” strain contamination of some BCG vials was confirmed [12].



**FIGURE 2** The disposition of infants born in Lübeck, Germany, during the 1930 bacille Calmette–Guérin (BCG) vaccination programme. Clin.: clinical; Radiol: radiological; Mtb: *Mycobacterium tuberculosis*; PME: *post mortem* examination; TB: tuberculosis, TST: tuberculin skin test; XRC: chest radiograph. #: PME refused by five parents, assessment by history, clinical and radiology findings.

By 14 July 1930, deaths appeared to segregate into four periods [21]. Of 159 infants immunised between 9 December 1929 and 27 March 1930 and 8–12 April 1930, 53 (33.3%) had died. Notably, there were as yet no deaths among 91 infants immunised between 28 March and 7 April 1930 and 14–25 April 1930; six deaths eventually occurred in the latter groups (six among 91 (6.6%) infants), suggesting that vaccine contamination had occurred even during relatively safe periods when fewer infants died.

A detailed, wide-ranging analysis taking into account death, but also disease severity and infection risk, classified clinical outcomes and BCG contamination into a range of steps of disease severity. Disease severity and death appeared associated with probable ingested dose of virulent bacilli, but it remained difficult to delineate clear-cut differences in disease occurrence and specific vaccination periods in individual infants [1].

### Epidemiological aspects of the Lübeck disaster

The first death of a partially vaccinated infant, at age 5 days as a result of prematurity, occurred on 31 March 1930. In April 1930, six infants died as result of tuberculosis. By end of June 1930, 47 infants had died and worse was feared. Intensive surveillance was planned until 1932–1933. However, in July 1930 there were 16 deaths and in August there were eight deaths. Thereafter, in one of the most striking observations resulting from the tragedy, the infant mortality rate declined dramatically; only six further tuberculosis-related deaths occurred from September to December 1930. No additional tuberculosis deaths occurred throughout the 5-year post-vaccination observation period. Viewed in terms of infant age, by completion of age 3 months 50% of eventual deaths had occurred and 87.5% by completion of age 5 months. No relapses or new tuberculosis manifestations occurred among survivors neither following a year after vaccination nor at time of publication of the final report in 1935. In 1942, Kleinschmidt followed up 122 survivors and had reliable information regarding another eight children; neither further tuberculosis-attributed deaths nor recurrences were observed [26]. The occurrence of death and the numbers of children presenting in Moegling's disease categories during the 3 years post-tragedy are summarised in table 1.

After careful reading of the pathology and microbiology reports, we revised the number of tuberculosis-attributed deaths from 72 [27] to 67; 10 deceased infants did not die of tuberculosis. Two neonates died of neonatal complications; the remaining eight died following accidents (two infants), other infectious causes and in one infant pylorospasms.

In 39 (15.5%) infants, no TST evaluation was undertaken. The remaining 212 (84.5%) infants were evaluated by percutaneous TST with Moro or Ektabin reagents. Overall, 190 (89.6%) responded positively to one of these TSTs; among the 22 (10.4%) with negative results, six infants were in disease severity group "6". Böcker commented that the remaining TST-negative infants may not have been infected with virulent bacilli. Interpretation of these results is further complicated by the fact that there is no doubt that oral BCG vaccination will lead to TST-positivity in a proportion of neonatally vaccinated infants and could also cause necrosis in lymph-node tissues and primary foci with subsequent calcification [28, 29]. It could therefore be questioned whether all the infants, with one exception, as claimed by Moegling, were fed contaminated vaccine.

**TABLE 1** Condition of the vaccinated infants at different time points between July 1930 and September 1933 (data from [1])

Disease severity group	1930		1931		1933
	July 1930	December 1930	April 1931	May 1932	September 1933
† Died	63 (25.1%)	74 (29.5%)	76 (30.3%)	77 (30.7%)	77 (30.7%)
1 and 2	22 (8.8%)	3 (1.2%)	0 (0%)	0 (0%)	0 (0%)
3	56 (22.3%)	34 (13.5%)	28 (11.2%)	0 (0%)	0 (0%)
4	66 (26.3%)	61 (24.3%)	76 (30.3%)	76 (30.3%)	6 (2.4%)
5 and 6	44 (17.5%)	79 (31.5%)	71 (28.3%)	98 (39.0%)	168 (66.9%)
Total	251	251	251	251	251

Classification of Moegling's grades of disease severity (from [1]). †: Death. 1: Seriously affected; likely death. 2: Seriously affected; doubtful prognosis. 3: Seriously affected, but prospect of improvement. 4: Affected by recognised milder complications. 5: No clinical signs but a positive tuberculin skin test. 6: No clinical signs and negative tuberculin skin test. Percentages in brackets are related to the cohort of 251 children.

No long-term complications were reported with the exception of six children with varying degrees of deafness following tuberculous otitis media. Further plans for intensive surveillance were consequently shelved.

### **Anatomical pathology findings**

Twelve early PME, before the nature of events was fully appreciated, were performed by local medical personnel and these results and clinical findings were reviewed by Schürmann; he was solely responsible for 53 PMEs and assisted at another seven [30]. Schürmann preferred reporting detailed findings of only PMEs in which he participated, consequently reports frequently refer to varying PME numbers providing only percentages regarding some findings.

### **Primary foci**

Given the gastrointestinal infection route, it was expected that almost any site accessible from the gastrointestinal canalicular system might have primary foci. The sites of primary foci among 60 infants for whose PME Schürmann was responsible are summarised in figure 3. The four main sites were the small bowel, the stomach and oesophagus, the oropharynx, and the lungs; multiple foci were common. In 50% of cases there were two loci, in 29.9% three, in 18.3% a single locus and in one infant (1.7%) there was a focus in each of the four loci.

Mesenteric nodal changes were identified by Schürmann in all 60 Lübeck infants in whose PME he participated and were accompanied by mucosal primary foci in 59 (98.3%). These changes varied from 70 ulcers to single foci only microscopically visible and were concentrated close to the ileocaecal valves within Peyer's patches. Mesenteric nodes were often greatly enlarged and already healing and calcifying soon post-infection; the earliest calcification being noted 140 days post-infection. In only one child with limited mesenteric nodal tuberculosis changes were no primary intestinal primary lesions found despite serial sections over 0.75 m of intestine.

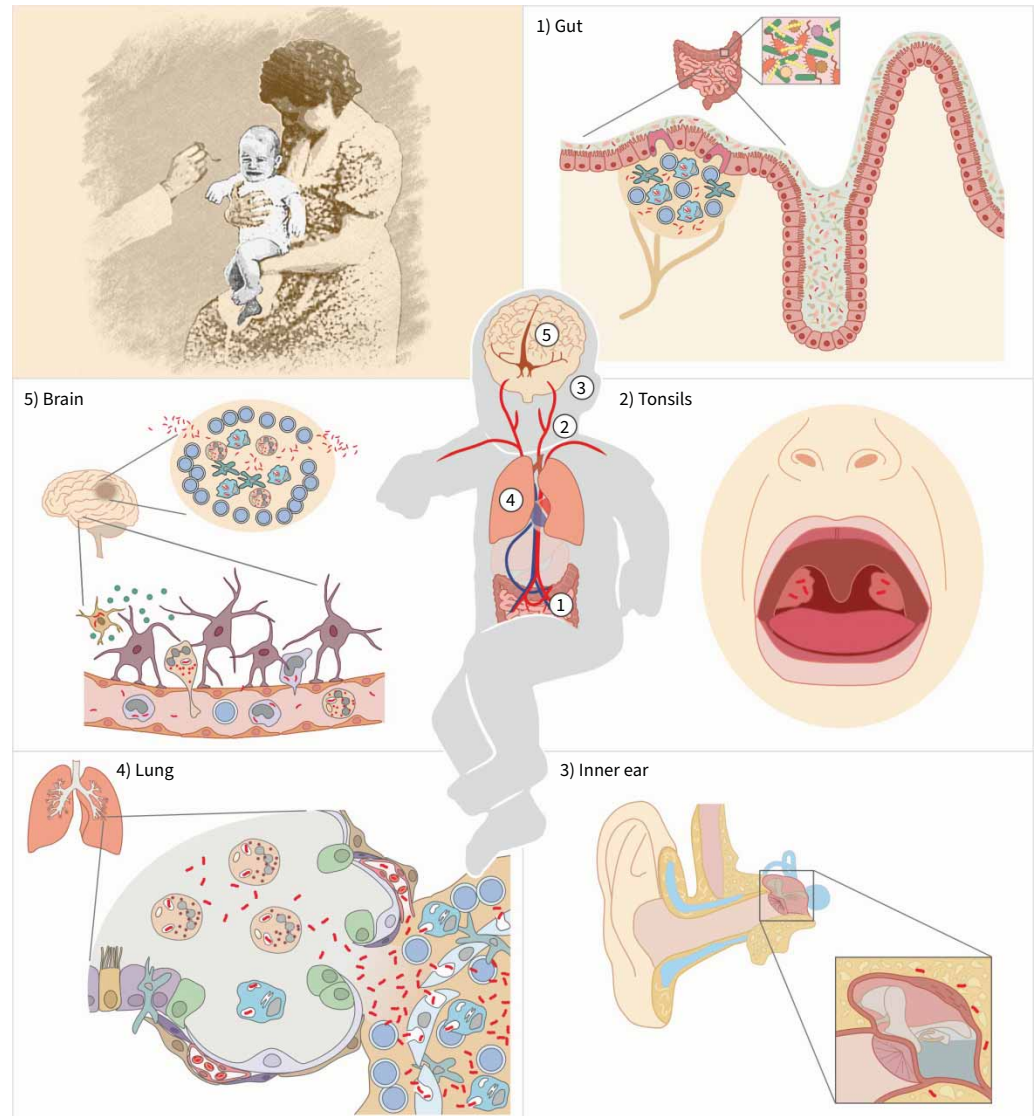
Even 44 days post-infection, fresh, deep intestinal wall ulcers might still be visible, but fibrotic changes were already developing; in older children who died 91–128 days post-infection, signs of healing were frequent and gut wall tuberculosis changes of primary foci more difficult to find. No primary foci were found distal to the ileocaecal valves. In older infants, secondary caecal or rectal ulcers were frequent, but unaccompanied by typical primary lymph node lesions.

The oesophagus, stomach and duodenum are usually considered relatively immune to tuberculosis and their frequent involvement was unexpected. The duodenum did appear relatively resistant to tuberculosis and a primary focus was present in only three (5.0%) of 60 infants. However, among 27 infants with tuberculosis lesions in the stomach, 11 (40.7%) lesions associated with regional nodal tuberculosis infection were clearly primary. Vomiting and retching causing mucosal tears might have facilitated establishment of these foci.

Similarly, oesophageal tuberculosis lesions were unexpectedly present in 11 (19.3%) of 57 infants; in three, regional lymph node involvement supported a primary focus diagnosis. As in the stomach, these lesions were ascribed to overwhelming infectious doses and mucosal damage following retching and vomiting.

The oropharynx was the second commonest site of primary foci. Tuberculous cervical lymph nodes were found in 52 (89.7%) of 58 infants on detailed PME. In six (11.6%), the features were those of post-primary tuberculosis, but in 46 (88.5%) they were part of a primary complex. The commonest sites of primary foci were the oropharyngeal tonsils where tuberculous changes were observed in 42 (80.7%) infants and the palatine tonsils with changes in 29 (55.7%). Changes were typical of a primary focus in 26 (50%) and 22 (75.9%) infants in the oropharyngeal and palatine tonsils, respectively. In one instance, the nucleus of a tooth harboured a primary focus. All oropharyngeal primary lesions were ulcerous, frequently involving tonsils, but oropharyngeal healing occurred rapidly and often leaving no macroscopically visible signs.

In two instances, death was accidental and oropharyngeal primary lesions were limited to small, calcified, deep cervical nodes found only on histological examination. One of these infants died 91 days post-infection and intestinal mucosal lesions were also found but were visible only on histology; however, in the mesenteric nodes, macroscopic, confluent, caseating, fibrous-enclosed lesions were present with scattered, scarce tubercles in the spleen; BCG was cultured from gastric-wash specimens. The second child died 498 days post-infection. All tissue cultures were negative and no intestinal wall lesions were noted, but several small centrally calcified caseous mesenteric nodes were found.



**FIGURE 3** The site of primary tuberculosis foci and secondary lesions in 60 Lübeck infants who died following ingestion of bacille Calmette–Guérin vaccine contaminated by *Mycobacterium tuberculosis* within 10 days of birth and closely examined during *post mortem* examination [30]. Foci were found: 1) in the small bowel in 59 (98.3%) infants and the stomach or oesophagus in 11 (18.3%); 2) in the oropharynx in 47 (78.3) infants; 3) in the tympanic cavity in six (10%) infants; and 4) in the lungs in 15 (20.8%) of 72 infants. 5) Secondary lesions arising as result of lympho–haematogenous spread were found in the brain in 34 (47.2%) of 72 Lübeck infants, of whom 19 (26.4%) had tuberculous meningitis at death.

Complex anastomoses involving all cervical nodes and lymph vessels were frequent, complicating identification of primary infection sites. Most often deep cervical nodes but especially the upper group were affected. Frequently affected nodes were bilateral, irrespective of the primary focus site. When lower cervical nodes were involved, there were often anastomoses with axillary nodes. Schürmann emphasised that nodes should be examined histologically; a tuberculous complex might be recognised only by histological examination.

Otitis media tuberculosis was present in 21 (29.2%) of 72 infants of whom nine (42.9%) died. An important potential consequence was petrous bone involvement leading to facial nerve palsy. This was found on PME in five children with tuberculous otitis media and was associated with a poor prognosis. Of nine children with tuberculous otitis media who died, five died as result of disseminated tuberculosis and four as result of tuberculous meningitis.

A primary pulmonary complex was present in 15 (20.8%) of 72 infants and more than one focus was found in five infants. Extensive thoracic lymph node enlargement and caseation was present in every case and the intestines and oropharynx had regional primary nodes at similar developmental stages suggesting simultaneous establishment of these foci. Frequently, the focus was clearly associated with a bronchus and caseous bronchitis often caused obstruction. Occasionally, main bronchi, and once the trachea, were compressed by surrounding nodes. The fluid nature of the infectious agent and spoon feeding probably contributed to the many primary lung foci in these very young infants. In six infants, their noses were held during vaccine administration; four vomited after all three vaccine doses. The finding of pulmonary primary lesions in 20% of deceased infants related to bronchogenic aspiration of ingested material is thus not surprising.

In two children, late secondary pneumonia with cavitation developed and some cavities contained stomach contents. Gastrointestinal stasis and reflux or vomiting associated with peritonitis, ileus or meningitis leading to aspiration probably caused these lesions. The absence of pulmonary nodal involvement indicated their secondary nature.

Among surviving infants, a pulmonary primary lesion was infrequent and detected on chest radiology in only 11 (6.4%) of 173-survivors.

#### **Lympho-haematogenous *M. tuberculosis* dissemination**

Generalised dissemination of *M. tuberculosis* outside the primary focal entry point was prominent. Schürmann examined 54 infants closely for features of lymphohaematogenous dissemination and reported such features in more than 60% of these infants involving lymph nodes, the spleen, the lungs, the liver, the bone marrow, the brain and its membranes, and the kidneys. In a minority of infants, the adrenal glands, the thyroid, the skin, the pancreas and hypophysis were infiltrated. The simultaneous involvement of multiple organs involving more than five systems was common and considerable variation in focal size of lesions suggested intermittent, repeated showers of bacilli, a condition best described as protracted haematogenous tuberculosis [31, 32]. In 23 (42.6%) infants, early generalised dissemination was sufficiently severe to be alone identified as cause of death 44–127 days post-infection.

Closely associated with lymphohaematogenous dissemination, tuberculous meningitis was a major cause of death; 19 (35.2%) infants had tuberculous meningitis at death, but in two the primary cause of death was respectively perforation peritonitis and bleeding from an intestinal ulcer. On PME, inconspicuous solitary foci, frequently caseous, or enclosing fibrosis or calcification were found lying in the brain substance, the choroid plexus or meninges or simultaneously in various stages of development or regression in several sites. In a further 15 infants, similar central nervous system lesions were noted but were not associated with development of meningitis. In some of these latter infants, calcification of the intracranial lesions was already developing.

Among the 19 children with tuberculous meningitis, frequent inflammation across the brain base and choroid plexus might have suggested that it was the main point of penetration into the cerebrospinal fluid (CSF), but Schürmann considered that despite the overwhelming nature of these lesions, the solitary caseous foci were more relevant for tuberculous meningitis pathogenesis and localisation of the majority of lesions at the brain base and in the choroid plexus was determined by CSF flow from an entry point at other sites.

The first symptoms of meningitis among the 19 children with tuberculous meningitis occurred 70–310 days post-infection while death occurred between 72–313 days post-infection.

#### **The immediate causes of death in the Lübeck infants**

Based on the PME findings in 72 Lübeck infants, lymphohaematogenous-disseminated tuberculosis was considered sufficiently severe to have alone caused death in 24 (33.3%) of the infants. Given the known susceptibility of infants to haematogenous spread of *M. tuberculosis* and its consequences this is not surprising [33, 34]. Seventeen (23.6%) infants died as result of tuberculous meningitis and a further two had meningitis at death, but the final cause of death was ileus and gastrointestinal haemorrhage, respectively. Gastrointestinal complications and their consequences, such as ileus, perforation peritonitis, intestinal haemorrhage and resulting anaemia and their consequences, difficult to diagnose accurately and manage with facilities of the time, caused death in 24 (33.3%) infants. The speed with which dissemination caused death is notable; the first death following widespread infection dissemination occurred 44 days post-infection; after 127 days, there were no further deaths directly attributable to dissemination.



### Radiological findings among survivors

Among the 173 surviving infants, only 11 (6.4%) had specific pulmonary tuberculosis radiological features that were typical of a primary lung complex [23]. In four cases, these changes were the sole abnormal radiological finding [23]. During the first 6 months post-infection, infiltrates, probably representing mild dissemination, appeared among a minority of surviving infants but regressed spontaneously. It was noteworthy that features of a primary complex were seen only in the first 2–3 months of life or when calcification appeared. Among surviving infants, abdominal radiographs 4 years post-vaccination were available from 173 (98.9%); in 126 (73%), calcifications were present, in 40 (31.7%) these were extensive, but in 86 (68.3%) they were slight. In only two cases was splenic calcification visible; there were no hepatic calcifications. Despite extensive abdominal calcifications among survivors, there were few associated clinical symptoms.

### The trial

Deycke and Alstaedt were charged with negligent manslaughter and the resulting trial lasted from October 1931 until February 1932. Its procedures were closely followed, not only in Germany, but also internationally. Both physicians were found guilty. Deycke was sentenced to 2 years and Alstaedt to 15 months imprisonment, respectively. It was found that Deycke had not followed the procedures recommended by Calmette in preparing BCG and failed to evaluate the prepared vaccine in animal hosts. The vaccine was also prepared in an inadequate laboratory where cultures of pathogenic mycobacteria were also maintained. One of the lessons learned was the necessity of a rigorous adherence to laboratory protocols. In this aspect the Lübeck disaster had an important effect on the development of scientific rigor and manufacturing protocols.

The tragical events in Lübeck also resulted in misgivings regarding the irresponsible and unethical manner in which certain aspects of medical research were carried out [35] and they continue to be part of an ongoing debate about the ethical aspects of medicine [36, 37].

### Discussion

Following his 1882 demonstration that *M. tuberculosis* was the cause of tuberculosis, Robert Koch favoured an aerogenous infection route [38]. This was supported by studies of Carl Flügge and George Cornett, the latter referring to aerogenous *M. tuberculosis* infection as “the common possession of all physicians” [39, 40]. Studies of pathologists provided further support [41–43]. Nonetheless, prominent researchers, including Calmette and von Behring, continued advocating a gastrointestinal route leaving no evidence of gastrointestinal mucosal primary infection and reaching the lungs following lymphohaematogenous spread, also without trace [44, 45]. At the time of the Lübeck vaccination accident, Stefan Engel, a leading figure in paediatric tuberculosis, was still promoting the cause of gastrointestinal primary *M. tuberculosis* infection spreading to the lungs [46].

Thus, a notable consequence of the Lübeck investigations was irrefutable evidence that despite likely high infecting bacillary doses, gastrointestinal infection spreading to the lungs occurred in only a minority of infants (20% of those dying in Lübeck). Further, the resulting disease features following either canalicular spread *via* a bronchus or lymphohaematogenous dissemination bore little resemblance to the already well-established, undisputed features of primary lung lesions [41–43]. Ulcerating, caseous bronchial changes and histories of choking and vomiting during vaccine administration further supported a bronchial aspiration path into the lungs in these infants.

Of equal importance was the demonstration of primary foci in the gastrointestinal mucosal wall in 59 (98.3%) of 60 closely examined infants; often very small and healing rapidly, such foci might be visible only on histological investigation. Anton Ghon considered that a diagnosis of primary gastrointestinal tuberculosis should be accepted only after histological examination [47]. This was disputed by others, but the very small size of many mucosal lesions and their rapid healing was seldom appreciated [39].

The considerable variation in the number of gastrointestinal primary foci and the number of different sites of primary foci was notable and speaks of variations in the infecting dose, as does the variation in mortality recorded during different periods of vaccination. However, linking these probable variations in infecting dose to death is almost impossible and death occurred in infants with only single primary foci as well as those with multiple foci. It is also noteworthy that early researchers documented that enormous repeated infecting doses in experimental animals were needed to establish a gastrointestinal infection compared to the very low numbers, often a single organism, needed to establish a respiratory infection [48].

At that time, it was also questioned whether gastrointestinal tuberculosis was associated with widespread infection dissemination [46]. This question was also resolved by the Lübeck investigations that clearly demonstrated the capacity of *M. tuberculosis* gastrointestinal primary infection to disseminate widely and rapidly on its own. Further support for this view was provided by contemporary studies of John Blacklock in Glasgow [49].

The second commonest cause of death in the Lübeck infants was spread to the meninges, the membranes surrounding the brain, in the form of tuberculous meningitis. The pathology findings associated with these cases have a particular resonance with the hypotheses of Arnold Rich and Howard McCordock, who i) denied any “direct” or “immediate” relationship between haematogenous miliary tuberculosis and tuberculous meningitis, and ii) failed to establish tuberculous meningitis by injecting *M. tuberculosis* bacilli into the circulation of experimental animals [50]. Nonetheless, paediatricians have remained impressed by the concordance of tuberculous meningitis and haematogenous-disseminated tuberculosis [51]. Knowing precisely when infection occurred among the Lübeck infants allowed accurate determination of time between infection and tuberculous meningitis onset and death; the latter varying from 72 to 313 days. In a similar incident, an unexpected series of 10 tuberculous meningitis cases was encountered in Neuenberg, Germany [52]. These were traced to a midwife with open pulmonary tuberculosis who applied mouth to mouth respiration to newborn infants with difficulty breathing. Of 10 resulting tuberculous meningitis cases, seven occurred 67–120 days post-birth. Similar findings were reported by others [33, 34].

From clinical and experimental evidence, it is known that the time after establishment of tuberculous lesions until caseation develops is approximately 50–60 days [53]. Tuberculous meningitis seldom occurs in infants less than age 2 months and in older children predictably occurs approximately 2–6 months post-infection [33, 34]. In the Lübeck infants, solitary caseating brain lesions were found in those with, but also without, tuberculous meningitis, as described by others [54]. This suggests that although caseation is the essential element in tuberculous meningitis pathogenesis it is a matter of chance whether a caseating lesion is suitably situated to permit penetration of mycobacteria into the CSF. It is also not always appreciated that haematogenous dissemination and miliary tuberculosis are often protracted, intermittent processes, as in many Lübeck infants. These findings clarify precisely the duration during which repeated waves of haematogenous dissemination establish a meningeal focus from which, after caseation, tuberculous meningitis can develop and why older established caseation in the “Rich focus” frequently accompanies the presence of fresh haematogenous lesions in brain tissues.

Moegling declared that the mortality rate of 28.7% post-neonatal *M. tuberculosis* infection was surprisingly low. However, we concluded that even fewer infants (67/251; 26.7%) died as result of tuberculosis. In a 1930 review of German infant mortality due to tuberculosis, Franz von Groer reported a mortality of 50–70% in infants with manifest tuberculosis [55]. Kleinschmidt reported a mortality of 50% among 44 infants with tuberculosis he had treated [56]. Thus, survival of over 70% of Lübeck infants indeed appears very good. Moegling ascribed this to the greater recovery of infants with abdominal and oropharyngeal lesions as compared to those with lung lesions. However, Kleinschmidt, reviewing the long-term follow up of Lübeck survivors in 1942, warned against underestimating the importance of abdominal infection and pointed out that 23 (31.9%) deceased infants died of “malignant tuberculosis dissemination” following gastrointestinal infection [26].

Moegling also hinted that infants with recent primary *M. tuberculosis* infection might have no features of active disease and might not even be recognised. Of note, the comparative figures quoted above record mortality of infants with manifest primary tuberculosis frequently requiring hospitalisation; hence, it might be more appropriate to assess Lübeck mortality in comparison to studies reporting the outcome of TST-positive or *M. tuberculosis*-infected infants without initial abnormal features. Several pre-chemotherapy-era studies, despite small numbers, provide a different perspective of the Lübeck mortality. Davies, describing a child contact study at the Brompton Hospital, London (1930–1952), recorded that among 29 children infected during the first year of life six (21%) died [57]. From clinical experience in the Mannheim Sanatorium, Margarete Röpke, reported five (21.7%) tuberculosis-attributed deaths among 23 infected infants [58] and others recorded the death of 16 (23.9%) infants among 67 infected [59]. These and similar reports suggest that mortality among the *M. tuberculosis*-infected Lübeck infants was not unduly low but within a range expected among groups of neonatally infected infants [60–62].

Tuberculosis remains a major cause of death in infants and young children in high tuberculosis-incidence communities [63]. Our review highlights the urgency *M. tuberculosis* infection of the very young creates. Within 3 months of vaccination infection, 50% of deaths had occurred, by 6 months more than 90% and, thereafter, the crisis was almost over with little evidence of later relapse despite lack of chemoprophylaxis.

The Lübeck findings provide an accurate measure of time within which one might expect active, serious forms of tuberculosis to develop in very young children post-infection that is mirrored by other pre-antibiotic-era reports [33, 34]. Edith Lincoln recorded that among young children 58% of deaths occurred within 3 months, 74% within six months of diagnosis and 90% within a year. More recently BEHR *et al.* drew attention to the tendency for active tuberculosis to develop relatively soon post-infection in children and adults, with few subsequent episodes [64]. The risk of tuberculosis was also recently reported among children age <5 years in close contact with an adult with microbiological or radiographically identified tuberculosis [65]. Among 247 contact children age <5 years with a positive TST or interferon-gamma-release assay who developed tuberculosis, disease presented in 238 (96%) within 90 days of initial screening. The institution of chemoprophylaxis in infants and very young children in contact with cases of infectious pulmonary tuberculosis is urgent.

Our review illustrates the significant role of the Lübeck disaster in clarifying aspects of the pathogenesis of tuberculosis. Evidence derived from the tragedy investigations clearly demonstrates that pulmonary primary *M. tuberculosis* infection was not the consequence of a subclinical, silent, gastrointestinal infection. It also provides a precise timeframe during which serious consequences of primary infection, such as lymphohaematogenous dissemination and tuberculous meningitis, are likely to occur emphasising the speed and frequency with which serious consequences can develop in infected very young children, without chemoprophylaxis.

The Lübeck disaster was not only a tragedy for the children, families and greater Lübeck community, but also for Deycke and Altstädt; intent on doing good a tragedy was engendered. B. Lange reviewing the events in 1932 quoted the state prosecutor at the resulting trial: “*In human life we forget there are unguarded moments when we do something mechanically or neglect something, without our later being called upon to give any account of our error*”; he added a quotation from 1 Corinthians 10:12 of the Bible: “*Those who think they are standing should be careful that they do not fall*” [66].

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