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Risk factors for tuberculosis

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ABSTRACT: ***Risk factors for tuberculosis. P.D.O. Davies.***

The risk of developing tuberculosis is dependent on both the risk of being infected and the risk of infection leading on to active disease. The former will depend on the incidence of tuberculosis in the community where the individual lives or works. The latter will depend on many factors impinging on the individual both genetic and environmental.

The greatest single risk factor for developing tuberculosis from infection is concurrent HIV infection. Where these two infections are prevalent tuberculosis case rates have risen dramatically and will continue to do so unless either infection can be curtailed.

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Keywords: Risk factor, tuberculosis, HIV, Aids, Genetic, Environment.

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Introduction

There are two distinct aspects to the risk of developing tuberculosis: the risk of becoming infected and the risk that the infection may go on to develop into disease. The risk of becoming infected will depend on the prevalence of tuberculosis in the community in which an individual is living. The risk of infection developing into disease is multifactorial but the healthy adult with no risk factors in terms of life-style and absence of medical risk factors probably runs less than a 5% chance of progressing from infection alone to disease. On the other hand the unfortunate individual who acquires HIV infection in an area where tuberculosis is rife, such as sub-Saharan Africa will run a greater than 30% chance of developing tuberculosis.

This paper is not intended as an exhaustive review of all the literature on the subject but aims to pick out the most important studies, which may not be the most recent, leading to firm conclusions on risk factors for tuberculosis.

Definitions

Tuberculosis infection, now termed Latent Tuberculosis Infection (LTBI), is characterised by the presence of bacilli within a host individual but with no evidence of symptoms or pathology [1]. The only evidence may be a positive tuberculin skin test or a positive QuantiFERON or ELISA blood test [2]. The presence of disease is characterised by symptoms due to tuberculosis with evidence of pathological changes, which may be anywhere in the body but usually the lungs. The diagnosis of tuberculosis may be suspected by the presence of symptoms and pathology but can only be confirmed by isolating, that is growing, the responsible bacillus: M. tuberculosis complex, from a specimen taken from the patient [3].

The current world problem

In fact about one third of the world's population is infected with the tubercle bacillus, 2 billion people, and each year eight million develop the disease of whom about 1.8 million die. Due to a combination of population growth and HIV/AIDS, the single biggest risk factor for infection leading on to disease, this number is increasing steadily by between 1.5 and 2% each year [4].

Historical aspects

Archaeological data show that tuberculosis has afflicted man for at least eight thousand years [5]. The disease was present in society in varying incidence but did not appear to be a major killer of the human race until the early nineteenth century. Evidence from England suggests that with the advent of the industrial revolution, in the late 18th and early 19th centuries, tuberculosis became a major epidemic killing roughly one in four of the urban population [6, 7]. The reason was chiefly horrendously poor housing coupled with a high density of population, so that the working population could easily walk to the factories. This, together with poor nutrition, resulted in a rapid spread of tuberculosis with widespread morbidity and mortality.

This may have represented the origin of the modern pandemic of tuberculosis. The high rates of tuberculosis present in Western Europe around the early 1800s were probably spread gradually to the rest of the world [8].

This resulted in a peaking of rates in North America in the 1880s, in African and Asia around the early 1900s and as late as the 1950s among the Unuit Indians of Northern Canada and the highland dwellers of Papua New Guinea [9].

Accurate statistics on tuberculosis mortality only became available with the advent of the re-

port of the Registrar General of England and Wales in 1840 [10]. From that time it would seem that the incidence of tuberculosis fell steadily at about 1.7% per annum for over a century with the exception of the years covering the two World Wars [11].

The risk of being infected with tuberculosis is therefore partly dependent on which year a person was born. Those born in 1920s, eighty years ago, in the UK, would be very much more likely to be infected over their lifetime compared with someone born in the 1980s [12, 13].

In Liverpool we conducted a tuberculin skin test survey which showed that a quarter of those over 65 had a positive skin test indicating previous infection compared with none aged under thirty five [14]. A positive skin test was independent of previous BCG. These findings are consistent with the theory that older people are more likely to be infected than younger because they have lived through a time of higher prevalence of disease.

The reasons for this steady decline for over a century are disputed but improved living conditions have certainly played a part and some form of natural selection may also have occurred [15].

If the pandemic theory of tuberculosis spread is correct then tuberculosis peaks were at their highest among the white population of Western Europe earlier than anywhere else, so the decline will have stared in this part of the world [9, 11].

Higher rates elsewhere in the world, to some extent, reflect the fact that rates peaked in these areas later so that rates have had less time to fall.

Geographical aspects

The reason for the wide disparity of rates across the globe seen currently is related to the way tuberculosis has moved across the globe as described in the previous section.

By far the greatest risk factor for infection across the globe is the incidence of tuberculosis in the community in which an individual was born and spent their early years (fig. 1). Individuals born in a part of the world with a very high incidence of disease such as Southern Asia or sub-Saharan Africa will have a very high risk of infection. Annual rates of infection can be calculated from sequential tuberculin skin test surveys or by testing different age groups of children and young people [16]. These have been shown to be especially high in Southern Africa [17].

The incidence of disease in a country of origin is reflected in the incidence of disease in these individuals on immigration to a developed country [18-20].

This can be seen very clearly in rates of disease by ethnic origin in the UK and in the USA [21-22].

Thus those immigrating from China to the UK have rates of disease about 10 times the rate in the indigenous white population (table 1), those from South Asia have rates about 20-30 times the white rate and those from Africa rates 80 times as great.

The sooner disease presents after arrival in the adopted country, the higher the rate of disease appears to be (table 2). Children born to immigrant communities have rates intermediate between those of the same ethnic group born in the country of origin and white children born in the UK.

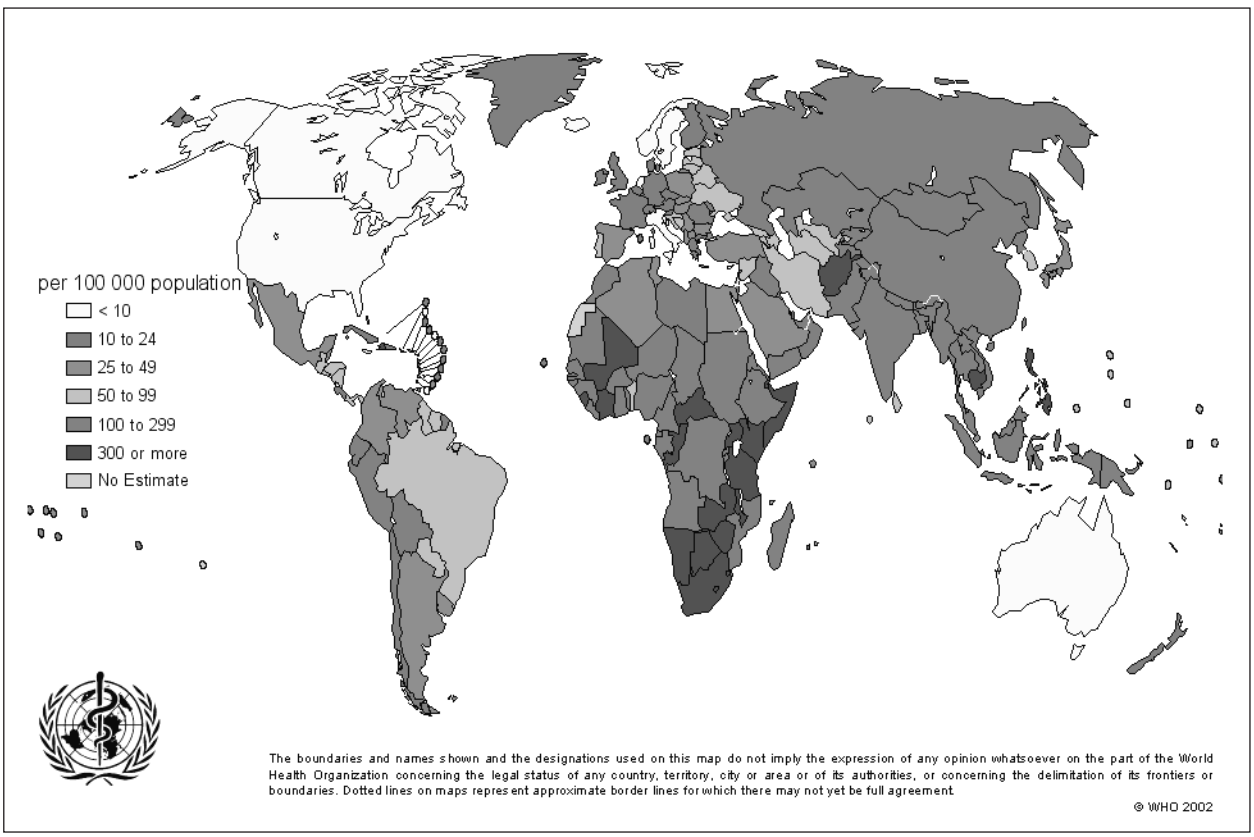

Fig. 1. - Estimated TB Incidence Rates, 2000.

Table 1. - Annual number of patients with tuberculosis and rate of disease in England and Wales by ethnic group - Reproduced from reference 21, with permission

	1988			*1993*			*1998*		
Ethnic group	*No**	*Rate***	*95% CI*	*No**	*Rate***	*95% CI*	*No**	*Rate***	*95% CI*
Black African†	77	64.4	58.1 to 72.2	355	151	140 to 164	743	210	198 to 225
Indian subcontinent	1784	132	128 to 136	2101	128	125 to 132	2141	121	118 to 124
Pakistani	528	115	109 to 121	841	155	148 to 164	826	143	136 to 150
Indian	1163	144	139 to 151	1133	125	120 to 130	1160	126	121 to 131
Bangladeshi	93	104	92.3 to 119	126	65.7	60.5 to 71.8	155	57.3	53.4 to 61.7
Chinese	48	36.2	32.8 to 40.3	41	30.7	27.8 to 34.2	103	77.3	70.1 to 86.1
Black Caribbean††	137	29.4	27.8 to 31.1	104	21.6	20.5 to 22.9	125	26.4	25.0 to 27.9
Black other‡	–	–	–	13	8.30	7.58 to 9.17	25	23.7	21.3 to 26.8
White	2504	5.36	5.33 to 5.39	2267	4.78	4.75 to 4.80	2108	4.38	4.36 to 4.40
Other/mixed¶	101	17.9	17.0 to 18.8	223	42.4	40.3 to 44.7	336	43.0	41.3 to 44.9
All	4659	9.383	9.334 to 9.433	5104	10.08	10.03 to 10.13	5658	10.93	10.87 to 10.99

*Numbers were multiplied by scaling factors (1.9384 for 1988; 1.886 for 1993) to give annualised figures for comparison.
**Rate per 100 000 population.
†In 1988 this group was termed "African".
††In 1988 this group was termed "West Indian and Guyanese".
‡In 1988 this term did not exist.
¶In 1988 this group included those described as "Arab"; this term did not exist in 1993 and 1998.
Note: four cases were missing ethnic group information in 1988; none in 1993; 77 cases in 1998.
Source of population data: 1988, 1993 and 1998 Labour Force Surveys.

Conversely areas of the world where tuberculosis has been allowed to decline over more than a century where living conditions have steadily improved and where little or no migration from developing countries has taken place, such as the northern Scandinavian countries have all but eliminated the disease [23].

Natural factors

Age

The year in which a person was born, and therefore the age of the person plays a crucial factor in the risk of being infected. Historically there seems to be a distinct pattern of risk of developing disease over a life time which has the shape of an inverted U. With the exception of the infant years risk of tuberculosis is lowest in later childhood but rises rapidly to peak at about age 25-35. Thereafter rates decline progressively. This picture may reflect a combination of increased risk of infection as the individual grows up and becomes independent, moving out of the house and becoming infected in the community [24].

It may also reflect the fact that susceptibility to infection developing into disease is greatest in young adults.

Work from South Africa suggests that rates in children aged 0-5 is 3.5 times higher than in adults. As it is unlikely that infection is more frequent in very young children than in adults, young children are very much more likely to develop disease from infection than other groups [25]. Mortality is also highest in these groups.

The lifetime risk of developing disease after infection is 43% in the first year of life, 24% between 1 and 5 years and 15% in adolescents compared to immunocompetent adults with a lifetime risk of 5-10% [26, 27].

A more recent study suggests that rates may increase again in older age groups, those over 65. Thus the "shape" of risk with age changes from and inverted "U" into a capital "N". This may indicate a natural decline in host defence with the ageing process [28].

Gender

The association of a tuberculosis risk factor with gender is more difficult to quantify. In some societies social stigma may preclude women from attending tuberculosis clinics and so accurate statistics on the incidence of tuberculosis by gender are difficult to calculate.

Historical evidence, from early in the 20th century suggests that women may have higher rates of tuberculosis than men in the young adult age group, 20-30, which may reflect increased susceptibility due to pregnancy [24]. By mid century females maintained higher rates than men did in the younger age groups but men appeared more susceptible in the older age groups. One worker has attributed this to the fact that males took up the smoking habit with World War I, which increased the risk of tuberculosis [29].

Contemporary evidence from the UK suggests that in the older age groups of the white population rates of disease in males exceed that of females by threefold [21]. This difference is not apparent in the Asian of Black African groups (fig. 2).

All evidence points to there being no gender difference in tuberculosis rates in the 1-14 age group. This suggests that if there is a genuine difference between the genders susceptibility it is not apparent until after puberty implying that hormonal differences may play a part.

Ethnicity

The difference between tuberculosis rates by ethnic group probably reflects the movement of tubercu-

Table 2. - Number of patients with tuberculosis and rate of disease by place of birth, year of entry to the UK, and ethnic group in England and Wales, 1998 - Reproduced from reference 21, with permission

	UK born			*Born abroad (total)*			*Born abroad (recent entrants)**			*Born abroad (longer residents)***			*Born abroad (year of entry unknown)†*	*Unknown/ missing place of birth*	*Total*
Ethnic group	*No*	*Rate††*	*95% CI*	*No*	*Rate†*	*95% CI*	*No*	*Rate†*	*95% CI*	*No*	*Rate†*	*95% CI*			
White	1784	3.89	3.86 to 3.91	219	9.85	9.61 to 10.1	55	12.6	11.9 to 13.4	79	4.42	4.30 to 4.54	85	105	2108
ISC	373	44.8	43.0 to 46.7	1656	177	170 to 184	411	359	323 to 404	875	106	102 to 111	370	112	2141
Black African	40	28.7	26.1 to 31.9	657	308	285 to 335	277	431	375 to 505	209	140	128 to 155	171	46	743
Black Caribbean	56	20.4	19.1 to 22.0	59	20.6	19.3 to 22.2	2	16.3	12.2 to 24.7	41	21.9	20.1 to 23.9	16	10	125
Other	55	9.50	9.1 to 10.0	362	82.1	77.8 to 87.0	143	114	103 to 128	131	41.5	38.9 to 44.5	88	47	464
Missing ethnic group				6			3						3	71	77
Total	2308	4.83	4.81 to 4.86	2959	73.6	72.3 to 75.0	891	118	114 to 124	1335	40.9	40.0 to 41.7	733	391	5658

*Arrived in the UK from 1994 to 1998.
**Arrived in the UK prior to 1994.
†High numbers of patients born abroad with unknown year of entry for some ethnic groups means that some rates for either recent entry or longer resident categories may be higher than stated.
††Rate per 100 000 population.
Source of population data: 1998 Labour Force Survey.

losis as a pandemic across the globe, starting with the industrial revolution and the very high rates this created in Western Europe. As Asia and Africa developed their peaks of high incidence up to 100 years after the white population of Western Europe with less time between the peak incidence and now, what might be termed "baseline" rates are seen to be higher in ethnic groups whose origin is from Africa and Asia [30].

Now of course other factors have come into play which have made rates in many groups of these origins very much higher still, notably poverty in Southern Asia and Africa and HIV/AIDS particularly in Africa but increasingly in South and South East Asia [4, 31, 32, 33]. It should be noted that this is not an inherent susceptibility due to race or ethnicity per se but to a combination of many factors which renders people living in certain areas more susceptible than others. It is probably a coincidence that this happens to be reflected most of all in ethnicity.

An example of this may be the comparison between black West Indians and Black Africans. Rates in the latter group are probably at least 20 times higher than the former, though both are inherently of very similar racial and therefore genetic background. Rates in the African group are so much higher because of an "accident" of place of residence [21].

In contrast in a study of people of different ethnic origin living in nursing homes and therefore presumably exposed to a similar risk of infection rates of infection and disease were twice as high in black than in white Americans, presumably indicating reduced natural immunity in the latter group. Within the relatively narrow confines of the same place of residence black individuals appeared to be twice as susceptible to infection as white people though once infected the chance of going on to overt disease was similar in the two groups [34].

Body build

The association of tuberculosis with body build has been well reviewed. It has been shown that lean underweight tuberculin reactors have a significantly higher risk of developing tuberculosis than persons of, or above, ideal body weight [35, 36, 37].

In a study carried out before World War II it was found that tuberculosis developed very much more frequently in men who were tall and thin than those who were short and heavy set [38]. In a controlled reading of chest x-rays it was shown that those who developed tuberculosis were thinner than those who did not [39].

In a study of 70,000 naval recruits morbidity was four times higher in those who were 15% or more underweight. Body build was not associated with tuberculin reactivity [40].

In a long term follow up of a BCG trial, reduced subcutaneous fat was associated with increased rates of disease [41].

A study from Norway showed a relative risk of more than 5 fold between the groups with the lowest and highest body mass index. The evidence for a link between tuberculosis and reduced body mass therefore appears to be very strong. To some extent this may compound other evidence of racial or socio-economic differences in risk [42].

Pregnancy

Accurate quantification of the risk associated with pregnancy is difficult [43]. There is certainly good anecdotal evidence to suggest that becoming pregnant increases a woman's susceptibility to tuberculosis [44]. The marriage of Charlotte Bronte was a matter of concern for her father as he feared that pregnancy could be fatal. As it turned out he was probably justified in these fears.

On the other hand alternative anecdotal evidence favours pregnancy as protective against tuberculosis [45]. A recent review of the data concluded that there was no real objective evidence for or against an association between tuberculosis increase and pregnancy. Provided diagnosis is made and treatment started promptly the outcome for tuberculosis in pregnancy is good [43].

The data does not support the theory that pregnancy is a major risk factor for the development of tuberculosis, though no well designed studies have been conducted.

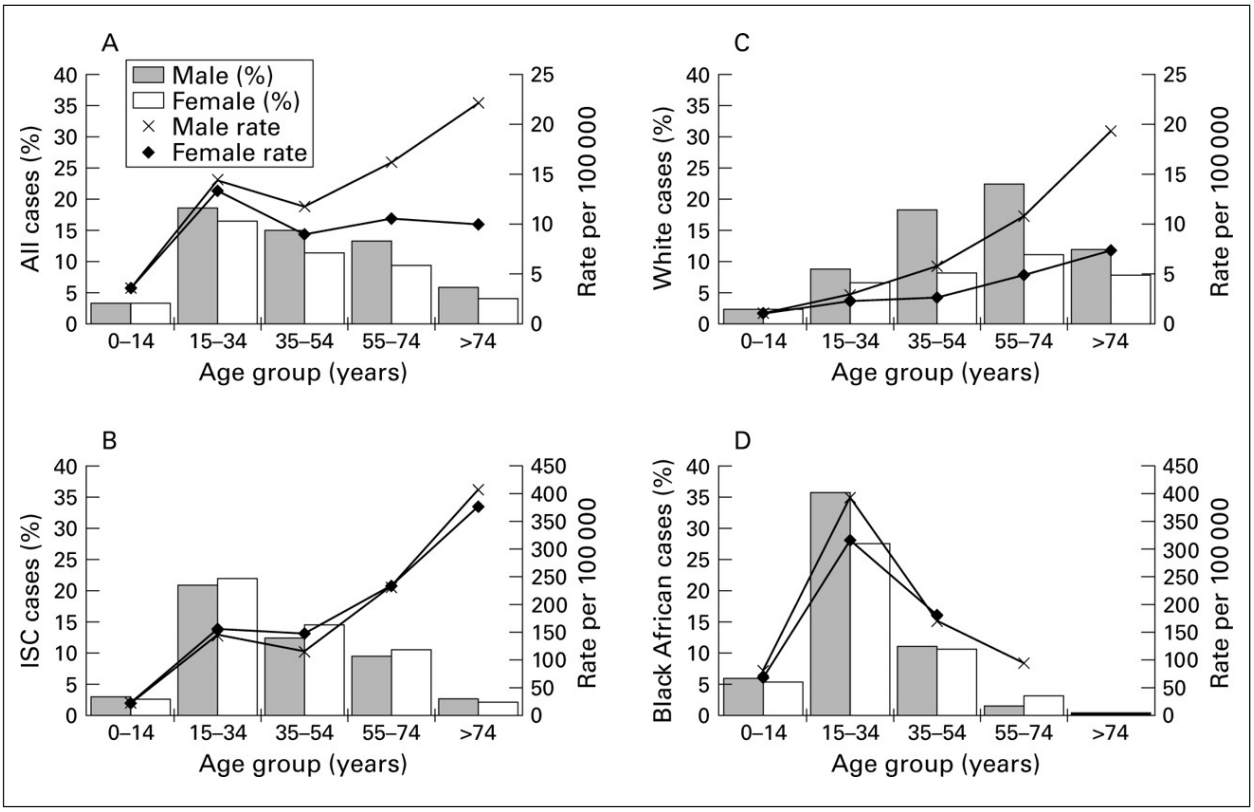

Fig. 2. - Rates and percentages of tuberculosis patients by sex and ethnic origin in England and Wales in 1998 [21]. Reproduced from reference 21, with permission.

There is evidence for a possible deleterious effect on tuberculosis in the puerperium if it is undiagnosed [46].

Life style

Occupation

As with most other factors to do with lifestyle, it may be difficult to tease out confounding factors such as ethnicity and poverty when assessing the risk of tuberculosis by occupation. Before the advent of chemotherapy nursing patients with tuberculosis was a well known risk for the disease [47]. With the introduction of specific chemotherapy the risk of acquiring disease by nursing and medical staff decreased considerably but in many studies has still been found to be present [48]. Of particular risk are mortuary technicians.

Miners and other workers in stone have increased risk through silicosis of the lung. (see below).

Poverty

That there is a very strong correlation between poverty and tuberculosis is not in doubt. Recent studies from the UK have shown a close correlation even in a Western city at the end of the 20th century [49]. What is less clear is the various aspects of poverty which may constitute the increased risk. It is likely that poor housing in terms of crowding leading to increased transmission and poor nutrition leading to diminished immunity are the two most important factors.

Within in the UK at least one paper has made the error of attributing the rise in tuberculosis to poverty because the rise was seen only in the poorest percentile areas of the country [50]. In fact this rise was probably due to the fact that recent migrants to the UK who had high risk because of their ethnicity, tended to move to the poorest areas.

Two separate studies has shown that ethnicity is more important than poverty as a risk factor in these areas [51, 52].

Within the socio-economically deprived population other factors may play a part. Residents in common lodging houses show increased rates [53-56]. Those who are homeless on the streets of London are at increased risk. Drug and alcohol abuse increase risk [57].

Diet

It is often difficult to control for factors related to poverty in order to study just one. A study of life-style factors of over 100 patients in Liverpool and over twice as many controls showed that controls tended to eat more salads and dairy products than patients [58]. It was also of interest that being on treatment for blood pressure seemed to be protective against tuberculosis. Body build was not assessed in this particular study but the tendency for raised blood pressure to be associated with obesity may have a compounding effect on relative protection from tuberculosis.

Smoking

The association between smoking and tuberculosis has been established for at least a decade. Original observations suggested that the change in the pattern of tuberculosis between men and women was due to the fact that men took up smoking after the First World War in large numbers whereas women did not [29].

More accurate studies by Doll and the life-style survey in Liverpool showed that those who smoked more than 20 cigarettes a day were between two and three times more likely to develop tuberculosis compared with never smokers [58, 59].

The same observation has been made in China and India [60-63]. Here tuberculosis has been shown to be the commonest cause of death in smokers: not an association we normally make in the developed world.

Drinking alcohol

Drinking is perhaps the most difficult of all factors associated with poverty to quantify risk for. This may be due to reluctance of patients to admit fully their alcohol consumption pattern and the presence of other factors, closely associated with alcohol abuse such as homelessness and smoking.

Poor nutrition and alcoholism go together to impair immunity. Evidence for the strict association between excessive alcohol consumption alone and tuberculosis is limited [64, 65].

Drug abuse

Apart from alcohol there is good evidence that misuse of other drugs particularly by intravenous drug users is associated with increased risk of tuberculosis. Again it can be hard to factor out other confounding variables [66].

Place of residence

As with other features related to poverty, place of residence may be inextricably linked with confounding variables.

In the 1980s work by Stead in the USA suggested that residents of homes for the elderly may be at increased risk [69]. It was suggested that with the declining immunity of old age and the close association of such individuals within residential homes, an increased risk was emerging. Though Stead was able to show this in his place of work in Little Rock Arkansas, other studies in the USA, UK and Hong Kong showed no such association [68, 69, 70]. Only in the study or residential homes for the elderly in Hong Kong was it shown that residents who had communal meals together were at increased risk [69].

Sunlight exposure

Sunlight exposure and Vitamin D supplementation were used as treatment for tuberculosis from the middle of the nineteenth century until specific chemotherapy became available. Recent work on the immunological mechanisms for Vitamin D, which have shown that the vitamin is important in macrophage activation, give credence to these methods [71].

It has been suggested that the lack of sunlight in the UK and other temperate areas is partly responsible for the high rates of tuberculosis, particularly non-respiratory tuberculosis found in migrants to the UK from South Asia [72].

The hypothesis is that these individuals acquire infection in their country of origin where sunlight is plentiful and Vitamin D levels high. Infection is therefore contained.

On moving to a country where sunlight is scarce, D levels fall and the previous efficient immune system in compromised. So active disease erupts. The parallel has been made to HIV infection acquired after tuberculosis infection also causing disease to erupt [73].

Specific protection

BCG

The science of BCG, the vaccine against tuberculosis, is fraught with controversy.

Studies carried out by the British Medical Research Council in the 1950s showed that BCG, when given to teenage school children gave about 75% protection for 15 years [74]. Since 1953 it has been national policy, in the UK, to vaccinate all children aged 12-13. Thus in theory the entire population receives some protection from early teenage years through to about the age of 30. The reason for choosing that age range was because in the 1950s cases rates were highest in young adults. The limited length of time for which BCG appeared to be protective would therefore be maximal at the age when most people suffered from the disease. Secondly the form of tuberculosis which pre-teenage children suffer from (primary) is not usually infectious, whereas the form suffered by adults is frequently infectious. Providing protection during early adult life would therefore reduced transmission.

In addition to the national policy for all teenagers, BCG is given at birth to those at high risk of disease; those with a family history of tuberculosis and those from minority ethnic groups.

Because of variation in trial results, most countries give BCG at birth to provide protection in the early years when infection can often lead to devastating widespread disease such as miliary tuberculosis or tuberculous meningitis. This is particularly important in high prevalence countries where the chance of being infected in very early life is high. Some countries such as the USA have chosen not to use it because most trials there have not shown any protective effect [75].

In 1994 a “metanalysis” of all the trials was published [76]. This looked at a total of 1264 articles, 70 in depth, 14 prospective trials and 12 case-control studies. The authors found that seven trials show a protective effect from death of 71%, five trials showed protection from meningitis of 64%, three, protection from disseminated disease of

78% and three, protection from laboratory-confirmed disease of 83%.

The authors concluded that geographical site of study explained 66% of variability.

They also found that on average BCG reduces risk of infection leading to disease by 50%.

This is probably an erroneous conclusion, as the efficacy of BCG cannot be averaged. Trials show it to be 80% protective in one place and 20% in another. Average efficacy should not be taken.

In terms of risk for tuberculosis it may be concluded that infants and teenagers, in the UK, who have had BCG, are probably at reduced risk of developing tuberculosis by about 75% for no more than fifteen years [75].

BCG does relatively little to reduce risk of tuberculosis across populations of all ages.

Medical factors

HIV/AIDS

Since it was first described it was apparent that HIV infection, by impairing cell mediated immunity, incurred a unique susceptibility on the patient to acquire tuberculosis (table 3). The epidemiology of tuberculosis has been completely altered in areas where HIV infection is prevalent, particularly in areas where tuberculosis was already endemic such as sub-Saharan Africa. One of the earliest studies to quantify the risk, carried out on intravenous drug addicts in New York showed that HIV-infected tuberculin positive individuals carried an annual risk of reactivation of 7.9% This estimates HIV infection to increase the risk of infection progressing to disease by approximately a hundred fold [77].

Cohort studies in African countries have shown that the annual risk of developing active tuberculosis in co-infected persons range from 5% to 15%, compared with a 0.2% annual risk form those not HIV infected [31].

Two studies from the USA, using techniques of molecular epidemiology, have shown that two-third of tuberculosis in HIV positive individuals was due to recent person-to-person transmission rather than reactivation of latent disease. In HIV infection recent infection rapidly leads on to disease [78, 79].

The strong association of tuberculosis with HIV in Africa has lead to the upsurge of tuberculosis in that region. Case numbers in Tanzania and Malawi increased by 5 to 6 fold between 1985 and 2000 [31].

In contrast there is evidence that patients with HIV seropositive tuberculosis are likely to be less infectious than HIV seronegative patients [80, 81]. This is probably because the type IV hypersensitivity response is reduced in HIV seropositivity reducing the likelihood of cavitation with concomitant high bacterial count in the sputum.

Silicosis

In addition to HIV infection other medical conditions increase the risk of infection leading to disease. Silicosis acquired as a result of working in mines or with stone has a relative risk of about 30 fold [82].

Immunosupressive treatment

Immunosupressive treatment will increase risk by suppressing the cell mediated immune response to infection with M. tuberculosis. Patients exposed to tuberculosis undergoing immunosuppression have very specific requirements for preventive therapy. In countries with high rates of tuberculosis, this is the commonest complication of renal transplant [83].

There has been recent interest in the new TNF-alpha blocking drugs used in the treatment of rheumatoid arthritis. These apparently increase the risk of tuberculosis infection developing into disease by approximately five fold [84].

Haemodialysis

Patients undergoing haemodialysis and those with chronic renal failure run an increased risk of 10 to 15 fold.

Gastrectomy and Jejunoileal bypass

Having had a gastrectomy or jejunoileal bypass increases the risk of tuberculosis by five and 30 to 60 fold respectively. The mechanism as to why this should be is not clear but may be related to nutritional deficiency.

Carcinoma

Cancer patients with head and neck tumours, malignant lymphomas, lung cancer, lymphosarcoma and reticulum cell sarcoma have up to a 16 fold increased risk.

Table 3. - Risk factors for tuberculosis following infection*

	Absolute/1,000 Person-years	Relative risk
Infection >7 years past	0.7	
Infection <1 year past	10.4	
HIV infection	79	
AIDS		170.3
Fibrotic lesion	2.0-13.6	
Silicosis		30
Immunosupressive Treatment		11.9
Haemodialysis		10-15
Gastrectomy		5
Jejunoileal bypass		27-63
Carcinoma of head or neck		16
Diabetes		2.0-3.6

* See Reference number 82.

Table 4. - Factors involved in susceptibility or resistance to tuberculosis and subject to genetically determined variation.

Factor or gene	*Function or mode of action*
Natural resistance-associated macrophage protein (NRAMP 1)	? Regulation of Phagosome cation levels.
Mannose binding lectin protein	Entry of mycobacteria into cells.
HLA-D	Antigen presentation.
Vitamin D	Macrophage activation.
Locus on chromosome 15	Unknown.
Locus on X chromosome	Unknown. May account for higher rates of tuberculosis in males.
Haptoglobin	? Regulator of lymphocyte function.
Km1 immunoglobulin allotypes	? Related to autoimmune tissue damage.
Various cytokines	T cell maturation and patterns of immune reactivity.

Diabetes

Diabetes in known to render the patient more susceptible to any infection. Tuberculosis has a 2-4 fold increase in these patients.

Genetic Factors

There have been many claims that populations and racial groups vary in their resistance to tuberculosis but it has been very difficult to separate the genetically determined factors from environmental ones. Nevertheless, several studies on monozygotic and dizygotic twins clearly indicate that inheritable factors are involved in determining susceptibility and resistance to overt tuberculosis after infection [85]. The human immune response to tuberculosis is multi-factorial, involving the uptake of tubercle bacilli by macrophages, class II HLA determined antigen presentation, activation of macrophages by T cell-derived cytokines and vitamin D [86, 87], granuloma formation and apoptosis of bacteria-laden cells. These processes are genetically controlled and several of the genes involved have been identified. Although much interest focused on the HLA genes, notably the HLA-DR2 and HLA-DQB1 loci, that determine which mycobacterial antigens are presented to the helper T cells [88, 89] interest has now largely shifted to non-HLA genes. Of these, two are of particular interest, the genes coding for the vitamin D receptor [86], and the natural resistance-associated macrophage protein (NRAMP1) gene [90]. The latter is the human equivalent of a gene found to determine resistance to intracellular parasites, such as *Leishmania* and *Salmonella*, in the mouse and it clearly affects human resistance to tuberculosis. Its function is unknown but there is evidence that it regulates the concentration of iron and perhaps other cations in the phagosomes of the macrophage.

Other genes affecting immune function have also been associated with resistance to tuberculosis [91]. These include genes determining the allotypes of the Km1 light chain immunoglobulin allotype [92], and of haptoglobin [93, 94], but it is not clear whether these are of prime importance or merely reflect gene linkage. Other genes currently under investigation include those affecting vitamin D levels (see below), the mannose binding lectin protein [95], and the various cytokines involved in protective immunity [96].

Although there have been a few examples of susceptibility to tuberculosis and other mycobacterial diseases within families associated with specific defects in gamma-interferon and other cytokines, family-based linkage studies and population-based case-control studies clearly indicate that resistance to tuberculosis is generally the result of a large number of genes inherited in a complex way [91]. The factors involved in susceptibility and resistance to tuberculosis that have been shown to very according to genotype are summarised in table 4.

Conclusions

Susceptibility to tuberculosis is multifactorial and complex. A better understanding of these will help to target screening of disease and allow preventive therapy to be given only to those at particular risk. This will help to harness resources to where they are most needed and prevent waste both in terms of reduced morbidity and mortality and in material.

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