Drivers of tuberculosis epidemics: The role of risk factors and social determinants

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ABSTRACT

The main thrust of the World Health Organization’s global tuberculosis (TB) control strategy is to ensure effective and equitable delivery of quality assured diagnosis and treatment of TB. Options for including preventive efforts have not yet been fully considered. This paper presents a narrative review of the historical and recent progress in TB control and the role of TB risk factors and social determinants. The review was conducted with a view to assess the prospects of effectively controlling TB under the current strategy, and the potential to increase epidemiological impact through additional preventive interventions. The review suggests that, while the current strategy is effective in curing patients and saving lives, the epidemiological impact has so far been less than predicted. In order to reach long-term epidemiological targets for global TB control, additional interventions to reduce peoples’ vulnerability for TB may therefore be required. Risk factors that seem to be of importance at the population level include poor living and working conditions associated with high risk of TB transmission, and factors that impair the host’s defence against TB infection and disease, such as HIV infection, malnutrition, smoking, diabetes, alcohol abuse, and indoor air pollution. Preventive interventions may target these factors directly or via their underlying social determinants. The identification of risk groups also helps to target strategies for early detection of people in need of TB treatment. More research is needed on the suitability, feasibility and cost-effectiveness of these intervention options.

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Introduction

The Commission on Social Determinants for Health (CSDH), set up by the World Health Organization (WHO) in 2005, has attempted to revitalize the debate and actions to improve health through addressing the “causes of the causes” of ill health. The commission has developed action frameworks in several fields to address the social determinants of health including early childhood development, globalization, urbanisation, employment conditions, social exclusion, etc. A key message from the CSDH is that public health achievements will largely depend on actions outside the health care sector (CSDH, 2008).

The work of the commission builds on a long social medicine tradition, from Virchow and the public health oriented social and environmental interventions that he and others inspired from the mid-19th century onwards (Rosen, 1974), through the social model of health adopted by WHO in the late 1940s (Chisholm, 1948), to the Health for All concept in the 1970s (WHO, 1978). It has not always been easy to keep the social medicine concepts and action frameworks alive (Amrith, 2002; Rosen, 1974). Several countries have tried consistently to pursue social policies aimed to promote equity in health, some with a great deal of success (CSDH, 2008). However, in most countries, little of the social model of health advocated by WHO and others was translated into practice. As a consequence, much preventable ill health and health inequity prevails today (CSDH, 2008).

The last 2–3 decades have seen reinvigorated attempts to fight diseases with medical technologies alone. Key concepts in today’s discourse on disease control include: evidence-based medicine; health systems strengthening; and community involvement. The latter two focuses mainly on the capacity to deliver medical technologies effectively. Meanwhile, social medicine has often been reduced to actions to identify risk groups that need to be targeted with medical interventions and attempts to influence individuals’ risk behaviour (Porter, 2006).

The current global tuberculosis (TB) control paradigm mainly focuses on cutting transmission through early case detection and effective treatment. Medical interventions are at the core of the global strategy (Lönnroth & Raviglione, 2008; WHO, 2006). However, historically, TB has been used as a prime example of a “social disease”, the control of which requires social, economic and environmental interventions. Furthermore, the need to control TB has often been used as an argument for improving living
conditions and reduce inequity (Chisholm, 1948; Rosen, 1974). After the second World War, a medically oriented TB control model emerged (Amrith, 2002). Much hope was initially placed on mass vaccination with BCG (Brimmes, 2007), hopes which were later shattered when it was demonstrated that the protective effect and epidemiological impact were limited (Rieder, 1999). When effective chemotherapy for TB became available in the end of the 1940 and beginning of 1950s, the control model switched to an almost completely curative focus. “Prevention starts with cure” became a slogan for the global role out of effective treatments. It was predicted that good coverage of effective treatment would result in a rapid decline in TB incidence (Styblo & Bumgarner, 1991). However, some recent observations have indicated that the impact of the present TB control strategy has been less than expected (WHO, 2008a). If these observations are confirmed, there may be a need to again broaden the strategy to include more preventive efforts (Farmer, 1997; Jaramillo, 1999). One avenue for improved TB prevention is the ongoing quest for better TB vaccines and better chemotherapy for preventive treatment. Another avenue leads through actions to address the social determinants of TB, as well as the more proximate risk factors (the physical and biomedical factors that directly influence the mechanisms that govern exposure to tuberculosis, risk of acquiring tuberculosis infection, and risk of progression from tuberculosis infection to active tuberculosis disease).

In order to assess the relevance and potential benefits of the latter, a review was conducted to identify key social determinants of TB and the possible causal pathways through which they operate. We also reviewed the historical and recent progress in global TB control with a view to assess the prospects of effectively controlling TB in the future with the current global strategy, and the potential to increase epidemiological impact through adding actions on social determinants and risk factors.

**Methods**

A literature review was undertaken to identify historic and recent trends in TB burden; social determinants of TB; and the most important proximate TB risk factors. We searched PubMed, the send-list “TB-Related News and Journal Items Weekly Update” (Centre for Disease Control and Prevention, Atlanta, USA), and a private data-base on tuberculosis publications from the past 40 years (created by Dr Hans Rieder). The analysis was carried out by the Stop TB Department at WHO, in collaboration with other relevant WHO Departments, including those responsible for tobacco control, nutrition, alcohol and substance abuse, environmental health, diabetes, and HIV/AIDS. The Priority Public Health Condition Knowledge Network of the CSDH provided technical support and feedback.

**Findings**

**History of TB epidemiology and social change in industrialized countries**

Epidemiological TB data before the 20th century is imprecise. However, some broad trends have been identified with a reasonable level of certainty. The conventional wisdom is that the incidence of TB increased in industrialized countries in the 17th to 18th centuries, peaking at different times in different places from the middle of the 1700s in Great Britain to the beginning of the 1900s in Japan. From these trends, a temporal association has been suggested between increased TB incidence and rapid industrialization and urbanisation. TB rates were often particularly high in urban areas. A plausible explanation is that transmission increased due to increased population density and crowded living conditions, while poor nutritional status and other risk factors increased the risk of break-down from infection to active disease in vulnerable groups, such as among the urban poor (Aparicio, Capurro, & Castillo-Chavez, 2002; Grundy, 2005; Rieder, 1999; Shimao, 2005). At the peak of the epidemic in Europe TB death rates were close to 1% per year in some urban areas, several times higher than the current rates in countries with high HIV prevalence (Fig. 1).

Throughout the 20th century, even before the introduction of effective chemotherapy, TB incidence declined steadily in most industrialized countries although it did increase temporarily during the two World Wars (Fig. 2). This was a period of economic growth, social reform, poverty reduction and improved living conditions as well as important advances in medicine and public health. The relative importance of the factors that may have contributed to the decline in TB in the 20th century is still a matter of debate. McKeown and Record (1962) suggested that before the 1950s the decline was due to improved nutritional status and to some extent improved living conditions, while medical and public health interventions had only a marginal impact before chemotherapy became available. Others have convincingly argued that the introduction of sanatoria and other mechanisms to isolate infectious cases as well as pasteurization of milk also had a significant impact on trends in the incidence of TB (Fairchild & Oppenheimer, 1998; Grundy, 2005; Lienhardt, 2001; Wilson, 2005). Natural selection may also have played a role (Davies, Tocque, Bellis, Rimmington, & Davies, 1999).

The discovery of the TB bacillus in 1882 was an outstanding advance in the understanding of transmissible diseases, and marked the beginning of the germ theory era. As a result of this discovery, a TB control paradigm based mostly on the biological understanding of the disease gradually emerged. It received a final boost with the discovery in the 1940s and 1950s of drugs that could cure the disease (Amrith, 2002). The expanded pharmacopeia of anti-TB drugs in the 1950s and 1960s helped to sustain and perhaps accelerate the decline in TB incidence (Fig. 2). But this was not only a period of rapid medical and health care advances. It was also a time of both rapid economic growth and accelerated welfare reforms in many industrialized countries (Navarro et al., 2006). Progress in TB control in the industrialized countries over the past centuries was thus brought about by advances on several fronts at the same time – medical, public health, economic and social.

**The evolution of the WHO’s TB control strategy**

After decades of TB control neglect, with sustained high TB burden in many low- and middle income countries and a resurgence of TB in several high-income countries in the 1980s, global
efforts to control TB were reinvigorated in 1991, when a World Health Assembly resolution recognized TB as a major global public health problem (WHO, 1991). The “DOTS” strategy was developed by WHO and partners as a response in the 1990s (Raviglione & Pio, 2002). Realizing that essential medical technologies for appropriate diagnosis and treatment were not used optimally in most parts of the world, the response was to devise a strategy that takes into account the basic health care elements required to effectively deliver those technologies. After a decade of DOTS implementation, the new “Stop TB Strategy” was launched in 2006 in response to a number of challenges that had not been sufficiently tackled through DOTS, notably the challenges of multi-drug resistant (MDR) TB and the intersecting epidemics of TB and HIV, as well as the challenges of weak health systems, insufficient engagement of private providers and communities, and reliance on imperfect device strategies that ensure good access to quality TB diagnosis and treatment for the entire population, especially the most vulnerable groups (Stop TB Partnership, 2006; WHO, 1994, 2002, 2005, 2006).

In summary, the Stop TB Strategy aims to control TB mainly by cutting the transmission chain, and this should be achieved by early and effective treatment of all people with TB. The strategy acknowledges that various social factors put certain vulnerable groups at high risk of developing TB and makes recommendations on ways to provide these groups with effective TB treatment. However, it does not explicitly address the underlying factors that make these groups more vulnerable to TB in the first place.

### Epidemiological impact of DOTS

Successful DOTS implementation was associated with a decline in TB incidence and prevalence in Peru, Cuba, China, parts of India, and the USA (China TB Control Collaboration, 2004; Frieden, Fujiwara, Washko, & Hamburg, 1995; Gonzalez, Armas, & Llanes, 2007; Suarez et al., 2001; Subramaniam et al., 2006). In some other countries in Latin America, including Chile and Uruguay, TB declined rapidly from the 1960s to the 1980s, which coincided with implementation of TB programmes that had the basic DOTS elements in place (Rodriguez De Marco, Sanches, & Alvarez Goya, 2007; Zuniga & Rojas, 2002). However, where there has been a demonstrable decline in incidence it has been difficult to separate out the effects of DOTS from those of social and economic development.

Recent country-level investigations of the impact of DOTS programmes have shown that, after several years of apparent successful implementation (as measured by high case detection and treatment success), incidence is not falling as rapidly as was expected. Vietnam appears to have reached the targets for case detection and treatment success since 1997, but the case notification rate has remained approximately constant over the last decade (Huong et al., 2006). The explanation for this is unclear. However, a recent study showed that a decrease in notification rates among older people has been offset by an increase among young people, especially young men in urban areas and remote rural areas (Vree et al., 2007). It is possible that internal migration and/or higher exposure to various risk factors for TB infection and disease in these young men has balanced out the impact of the control programme. In Morocco also, the reduction in notification rates has been less than expected considering the successful implementation of the DOTS programme for many years. Here too the problem seems to be related to increasing rates of TB among young men in urban areas (Dye, Ottmani, Laarsi, & Benchekih, 2007). Similar patterns are also seen in the routine surveillance data from Sri Lanka and Myanmar (WHO, 2007). Several States of India have been successfully implementing DOTS since 1998 but there has been no detectable decline in case notification rates (Watt, Hosseini, Lönnroth, Williams, & Dye, 2008). These observations raise the possibility that the impact of improved diagnostic and treatment services is offset by maintained or increased vulnerability to TB infection and disease among certain subgroups of the population.
The slower-than-expected rate of decline might also be because many people with TB are diagnosed so late that they have already infected many people before effective treatment starts (Porter & Grange, 1999; WHO/EMRO, 2006; WHO/WPRO, 2004).

The epidemiological challenge ahead: the role of prevention

The uncertainty about the impact of DOTS on the burden of TB is reinforced by a recent analysis of predictors of TB case notification trends between 1997 and 2006 (Dye, Lönnroth, Jaramillo, Williams, & Raviglione, in press). This analysis suggests that the variation in TB trends is more strongly associated with biological, social and economic factors than with NTP performance. Moreover, recent calculations suggest that, although prevalence and death rates are falling globally, the rate of decline is not fast enough to meet the MDG related targets to halve TB prevalence and death rates by 2015 compared to 1990 levels (WHO, 2009). The biggest challenges in cutting TB burden are in sub-Saharan Africa and Eastern Europe. The countries of sub-Saharan Africa and in Eastern Europe and the former Soviet Union showed striking increases in TB burden during the 1990s, for somewhat different reasons: in Eastern Europe and former Soviet Union countries, the resurgence of TB (after decades of steady decline before the 1990s) can be explained by economic decline and the failure of TB control and other health services since 1991, along with other factors such as social deprivation, poor living conditions, alcoholism, and the mixing of prison and civilian populations (Leon et al., 1997; Pesut, Gledovic, Grgurevic, Nagorni-Obradovic, & Adzic, 2008). In Africa the increase was largely due to the rapid spread of HIV in the 1980s and 1990s (Corbett et al., 2003). Reducing the burden of TB in these two regions will depend to a great extent on dealing with the factors that drove the burden of TB up so rapidly in the 1990s (WHO, 2008a).

In 2006–2007, the decline in global TB incidence was estimated at less than 1% per year (WHO, 2009). To eliminate TB by 2050 the incidence rate must fall by an average of 16% annually over the next 40 years (Fig. 3). Recent modelling suggests that even if the Global Plan to Stop TB is successfully implemented and results in the expected rate of reduction in incidence of about 6%, the global incidence rate in 2050 would still be of the order of 100 per million population, i.e. about 100 times greater than the elimination target (Watt et al., 2008). An incidence decline of >15% per year might be achieved temporarily through massive efforts to scale up of curative services, which would reduce transmission of TB. However, it is unlikely to be sustainable without additional efforts to prevent progression from infection to disease. Currently, more than 2 billion people are infected with Mycobacterium tuberculosis. As transmission falls, a growing proportion of cases arise from the reactivation of latent infections, rather than from progression of recent infections. A recent analysis of the reasons for slow decline in TB incidence in Hong Kong, despite good TB diagnosis and treatment services for several decades, suggests that high prevalence of TB infection among elderly combined with very high risk of reactivating contributes to a sustained high incidence (Vynnycky, Borgdorff, Leung, Tam, & Fine, 2008).

In summary, to achieve the long-term targets for TB control, efforts to cut transmission need to be complemented with interventions that reduce progression to active TB disease. Such interventions may include better preventive chemotherapy, a new vaccine that prevents progression from infection to disease, as well as interventions that reduce exposure to various social, environmental and biological risk factors for TB.

Proximate risk factors and upstream determinants

The socio-economic gradient

The TB burden follows a strong socio-economic gradient between countries, within countries, and within communities, and the poorest have the highest risk (D’Arcy Hart, 1934; Hanson et al., 2006; Harling, Ehrlich, & Myer, 2008; Hinman, Judd, Kolnik, & Daitch, 1976; Holmgren & Crosby, 2004; Lopez De Fede, Stewart, Harris, & Mayfield-Smith, 2008; Muniyandi et al., 2007; Van Rie et al., 1999). Studies assessing the burden of TB in specific vulnerable populations such as prisoners, the homeless, and certain ethnic minorities also show that there is a strong association between social deprivation and TB risk (Bobrik, Danishevski, Eroshina, & McKee, 2005; Buskin, Gale, Weiss, & Nolan, 1994; Friedman, Williams, Singh, & Frieden, 1996; Keppel, 2007; Mori, Leonardsun, & Welty, 1992; Rieder, 1999). However, the causal pathways linking poverty and low socio-economic status to increased risk of TB are not fully understood.

Proximate risk factors

Proximate risk factors include those that directly increase exposure to infectious droplets. A necessary risk factor for TB infection is contact with a person with active disease. The likelihood of having such a contact is determined by the underlying disease burden in the community. People living or working in environments where TB prevalence is particularly high are obviously at high risk of infection, for example prison staff and inmates (Bobrik et al., 2005) and certain health care workers (Menzies, Joshi, & Pai, 2007). The risk of exposure is also determined by the physical environment in which the contact takes place, including aspects of crowding, air flow and humidity (Rieder, 1999).

Proximate risk factors also include those that impair the host defence against infection and break-down to disease, such as HIV infection (Corbett et al., 2003), malnutrition (Cegielski & McMurtry, 2004), tobacco smoke (Lin, Ezzat, & Murray, 2007; Slama et al., 2007), indoor air pollution caused by burning of solid fuels (Lin et al., 2007; Rutherford, 2006), alcohol abuse (Lönnroth, Williams, Jaramillo, & Dye, 2008), silicosis (Corbett et al., 2000; Rieder, 1999), diabetes (Stevenson et al., 2007), malignancies, a wide range of chronic systemic illnesses, and immunosuppressive treatment (Rieder, 1999). There is some evidence that outdoor air pollution is a risk factor for TB (Cohen & Mehta, 2007; Tremblay, 2007). Depression and stress can have negative effect on the cell-mediated immune system and could therefore in theory increase the risk of TB (Prince et al., 2007).
In an analysis applied to the 22 High TB Burden Countries (HBC, countries that together suffer 80% of the estimated global TB burden), the population attributable fraction (PAF) for selected TB risk factors for impaired host defence was roughly estimated (Lönroth & Raviglione, 2008). This analysis, which was recently updated based on new estimates, suggests that malnutrition (PAF, 27%), smoking (23%), HIV (19%), diabetes (6%), harmful alcohol use (13%) and indoor air pollution (26%) are all important risk factors globally (though the evidence base for indoor air pollution is still weak). Their relative importance depends on the prevalence of exposure and is therefore different for different countries and regions. For example, a regionialized PAF analysis suggests, as expected, that HIV is a much more important risk factor in the Africa (PAF, > 50%) than elsewhere due to the high prevalence of HIV.

Links between socio-economic status and proximate risk factors

It is reasonable to assume that the higher risk of TB among people in low socio-economic status (SES) groups is largely an effect of their greater exposure to some or all of the risk factors discussed above. A recent multi-level analysis of TB risk factors from South Africa found an association between the risk of TB and smoking, alcohol and under-nutrition. These factors partly explained the underlying association between low SES and TB risk, suggesting that these proximate risk factors are on the causal pathway between poverty and TB risk (Harling et al., 2008). People from low SES groups have on average: more frequent contact with people with active TB disease; higher likelihood of crowded and poorly ventilated living and working conditions; limited access to safe cooking facilities; more food insecurity; lower levels of awareness and/or less power to act on existing knowledge concerning healthy behaviour (e.g. safe sex, smoking, diet and alcohol use); and limited access to high quality health care (FAO, 2006; Gilson, Doherty, Loewenson, & Francis, 2007; Kjellström et al., 2007).

Malnutrition and indoor air pollution are direct markers of poverty (FAO, 2006; Rhefuess, 2006). Smoking prevalence is consistently higher among the lower SES groups than among higher SES groups in all regions of the world and smoking prevalence is increasing rapidly in low income countries, while it is decreasing in high-income countries (WHO, 2008b). For HIV, alcohol and diabetes, the picture is more complex. On average, HIV prevalence is higher in poor countries than in rich countries and the prevalence is higher in countries with more unequal wealth distribution. However, there is wide variation in national HIV prevalence across countries with similar level of national wealth (Piot, Greener, & Russell, 2007; Reidpath, 2008). Furthermore, on an individual level the association between SES and HIV prevalence is generally higher among the better off than among the worse off in poor countries. However, within countries, at least for men, harmful drinking patterns and alcohol related morbidity and mortality follow a reversed socio-economic gradient: those with low SES are at highest risk (Schmidt, Måkelä, Rehm, & Room, 2008). The association between SES and diabetes is also complex. Economic development, reduced poverty and improved food security can lead to increased diabetes prevalence. The prevalence is generally higher among the better off than among the worse off in poor countries. However, in middle- and high-income countries the reverse is true. Here, people from low SES groups have higher prevalence, and this is probably linked to a less healthy diet and less physical activity (Irwin & Whitling, 2008; Smith, 2007).

The role of urbanisation

Rapid urbanisation can create ideal conditions for TB epidemics to flourish, unless accompanied by good urban planning, social reforms, environmental protection, and a strong and well-coordinated urban health system (Kjellström et al., 2007). TB incidence is generally higher in urban than in rural areas (Lönroth, Zignol, & Uplekar, 2006), and, as discussed above, there are signs that urban TB control is particularly challenging (Dye et al., 2007; Watt et al., 2008; WHO, 2007). The tendencies for the burden of TB to be higher in urban than in rural areas may be due to high population density, crowded living and working conditions, as well as lifestyle changes associated with urban living. Exposure to certain TB risk factors such as smoking, alcohol abuse, unsafe sex, and unhealthy diet, may increase when absolute poverty falls at the same time as rapid socio-cultural transitions lead to changed health behaviour patterns (Kjellström et al., 2007). Such changes are partly the result of globalization (Raviglione, 2007). For example, globalization of nutrition makes foods with high calorific value but a low nutritional value available at relatively cheap prices (Labonté, Blouin, & Chopra, 2007). Changed nutritional patterns combined with less physical exercise due to poor urban planning and lack of health promoting policies can explain why diabetes can coexist with malnutrition in poor urban settings (Kjellström et al., 2007). HIV prevalence is on average 1.7 times higher in urban than rural areas (UNAIDS & WHO, 2006), and this is linked to various social determinants of unsafe sex. The potential increase in risk increase due to clustering of these TB risk factors is often further augmented by fragmented health care systems in urban areas, and poor health care access among urban slum dwellers (Lönroth et al., 2006).

Discussion

This review suggests that, in order to reach long-term TB control targets, the current TB control strategy needs to be complemented with efforts to address TB risk factors and social determinants. Fig. 4 presents a framework for identifying entry points for such interventions. In principle, reducing the prevalence of the proximate risk factors will reduce TB incidence. This may be achieved by tackling these risk factors directly, or the social determinants – on the individual, community, national and international level – that lay behind them.

We know from the history of TB that general socio-economic development can contribute substantially to TB control by improving living and conditions, nutrition status, and health care services. However, economic development may also be associated with increased risk of TB, for example due to urbanisation and lifestyle changes. The dynamics of the relationship between socio-economic development and TB epidemiology, and the causal pathways that link SES with risk of TB are not fully understood. Fig. 4 is therefore indicative only, and may be used also as a framework for further research. The following areas of research require attention:

![Fig. 4. Framework for proximate risk factors and upstream determinants of TB.](image-url)
Basic epidemiological research to further establish causality and the strength of association for proximate TB risk factors. Refined country-specific analyses of population attributable fractions of different risk factors, accounting for interaction and heterogeneity across countries. Multi-level analyses of causal pathways linking low SES with higher risk of TB. Analysis of factors determining variation in TB burden and historic change in TB burden across countries and across geographical areas within countries. Modelling of the epidemiological impact of different scenarios for socio-economic change and change in risk factor exposure in populations.

While waiting for such analyses, available data points to the following actions:

First, the sine qua non of TB care and control remains high quality diagnostic and treatment. Additional efforts can be made to ensure that the most vulnerable groups of the population are reached with available medical technologies in order to stop transmission where it is most deleterious and in order to make available preventive chemotherapy to those at highest risk of progressing from latent infection to active TB disease. This will require mapping of high-risk groups and access barriers on national and sub-national levels, and tailoring of interventions strategies accordingly.

Second, NTPs could strengthen collaboration with other public health programmes in order to contribute to the prevention, treatment and management of HIV, malnutrition, smoking-related conditions, diabetes, and alcohol abuse. Frameworks for such work are already well established for HIV (WHO, 2006), and on the way for smoking (JUATLD & WHO, 2007). Good collaboration between public health programmes ultimately requires a well-functioning primary health care system. Contribution to health systems strengthening, already on the agenda for TB programmes (WHO, 2006), can help not only to improve diagnosis and treatment of TB, but also help to address these TB risk factors.

Third, and perhaps most challenging, interventions outside the health sector will have to be strengthened. Priority public conditions share many “upstream” social determinants. The further upstream the entry point for intervention, the more widespread the effect. The CSDH has developed frameworks for action to address a wide range of upstream social determinants (Blas & Sivasankara, 2009; CSDH, 2008). NTPs and the international technical partners supporting them need not re-invent the wheel but should support the full implementation of these frameworks. Political commitment – the first element of the Stop TB Strategy – should not only concern commitment from Governments to invest in and support TB diagnosis and treatment programmes, but also commitment by all political actors, including civil society, to address the upstream drivers of the TB epidemic.

Competing interests

The authors are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the World Health Organization. No external funding was provided for this research.

References
