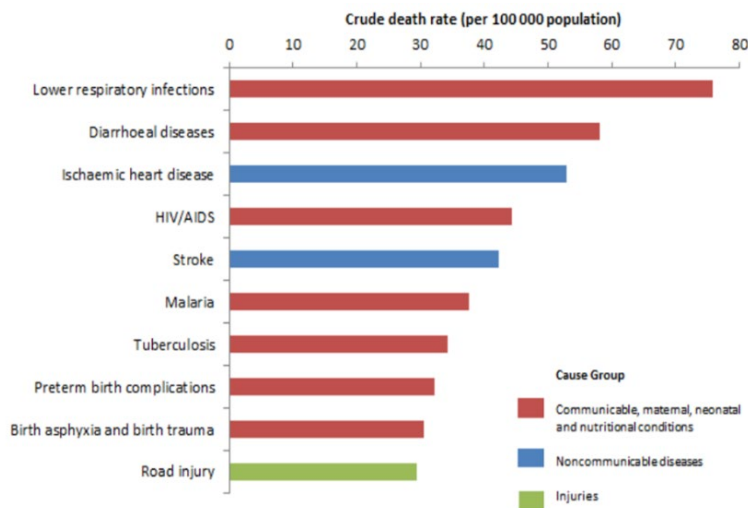


INFECTIONS OF THE LUNG AND HEART

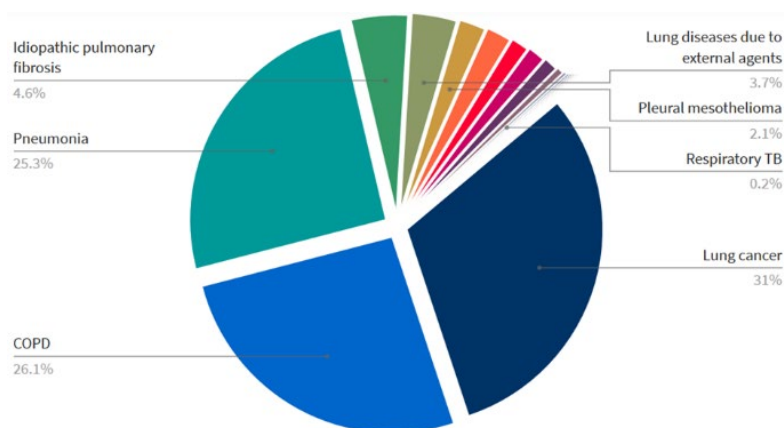
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The Lungs

The main function of the lungs and heart is to move oxygen from air into the tissues and CO₂ out again. For the lungs this means that they need to have a very large surface area (up to the size of a tennis court) pumping large volumes of air which is exposed to a very thin set of cells. Potentially this provides substantial opportunity for infections to enter the body. The lung has multiple layers of defence, which includes the epiglottis, the cough reflex, the mucociliary escalator, and various elements of the immune system. In this talk I will concentrate on infections in the lower respiratory tract (LRI/LRTI) or which compromise breathing. These can be within the respiratory tract itself such as pneumonia, between the lungs and the chest wall, or affecting the chest wall itself.



Infections of the lungs are among the top 10 causes of death in both low and high-income countries. The most important of these is pneumonia. This can be caused by bacteria, viruses and occasionally fungi. It is very common with up to 450 million cases a year globally. In the pre-antibiotic era it killed people throughout their lives. Now deaths tend to occur in the very young, the very old, the very poor and the immunosuppressed. Figure 1 (WHO data) shows the top 10 causes of mortality in lower income countries: lung infections are in top position.



Other than age and poverty the risk factors for pneumonia are smoking, air pollution, other health conditions (both of the lung and more generally), or weakened immune system. Around a quarter of lung-related deaths in the UK, as a typical high-income country, are pneumonia (Fig 2, British Lung Foundation data) and in this setting most are older adults. There is a strong correlation between pneumonia and age. After the first years of life when there is a moderately high chance of pneumonia, the probability of pneumonia falls

rapidly but rises in peoples 60s and 70s and is substantially increased in peoples 80s.

The most common bacterial pneumonia is pneumococcal pneumonia (*Streptococcus pneumoniae*). It is usually a lobar pneumonia meaning it affects one or more lobes of the lung with the other ones being relatively spared. If the



most common pneumonia cause of mortality in adults and children and can usually be treated with antibiotics provided it's caught early enough. Antibiotic resistance is a clear and present danger.

There have been significant changes in pneumococcal pneumonia due to vaccination over the last two decades. A 7-valent vaccine against pneumococcal infection was introduced in the UK in 2006, and has begun to be deployed elsewhere as well. This led to falls of the vaccine type invasive pneumococcal disease, of which pneumonia is numerically the most important, by 86%. It did however lead to other forms of pneumococcus rising and a new 13-valent vaccine was introduced. They led to a significant reduction of pneumococcal disease in children and also, largely through childhood reductions, in elderly adults, and this has led through to fewer cases of pneumonia.

There are around 700,000 deaths from pneumonia in children under five globally but this has been reducing rapidly. Here pneumococcus remains the most important cause but the second most important bacteria in young children (not adults) is (or was) *Haemophilus influenzae* type b (Hib). Hib vaccination was rolled out across high income countries and is now widely deployed in low-income countries in combination with other infections in the pentavalent vaccine. The results of a combination of better living standards and vaccination mean that under five deaths due to pneumonia have decreased by an estimated 37% from 2005 to 2015. This is contributed significantly to the rapid reduction we have seen in childhood mortality globally.

Although pneumococcus, and Hib in children, are the most important bacterial causes in terms of mortality there are a number of atypical bacterial pneumonias of which the most common are not susceptible to the same antibiotics. These include mycoplasma and legionella. Viruses make up the large portion of pneumonia with a much smaller proportion of deaths. An important virus in children in particular is the respiratory syncytial virus (RSV) contributing 5 to 7% of childhood pneumonia deaths globally. Currently there is no vaccine. Influenza is also an important cause of viral pneumonia and its importance varies by season and year. Typically it is less than 2% of pneumonia deaths but can be much higher with virulent and transmissible strains. In severe pneumonia from influenza the initial viral infection can be followed by a secondary bacterial pneumonia and in the 1918 flu pandemic this contributed substantially to mortality. Fungal lung infections are much rarer. They are most common as a significant pneumonia when people are immunosuppressed for some reason. And they tend to be associated either geographically or with particular occupations or activities such as caving in places where there are bats.

Tuberculosis is still one of the top 10 causes of death worldwide. It was common everywhere killing people in all walks of life (and was popular cause for heroines of operas and literature to die). It is now much more highly concentrated globally. The major drivers are poverty, HIV, drug resistance and some specific risk groups including people in prisons and those who undertake mining. Pulmonary tuberculosis is 85 to 90% of cases and causes almost all transmission. After an initial infection reaches the alveoli in most cases mycobacteria are surrounded by macrophages which are part of the immune system and walled off. This causes latent TB and may affect a quarter of the global population. Without treatment or HIV around 5% will develop disease in the first couple of years and 5% develop disease later in life. This may be open TB where the mycobacteria are seen in sputum down a microscope (smear positive); this is much more infectious. There are also cases which cannot be seen but grown subsequently or are detected by newer methods in the lab (smear negative TB).

Without treatment smear positive TB had a mortality of around 70% over 10 years and smear negative a mortality of around 20%. The key to pulmonary TB treatment is early diagnosis, and then six months of directly observed multidrug treatment. The first effective drug, streptomycin was developed in 1946. Most people now take three or four drugs for prolonged period. There have been recent improvements in diagnosis of TB. Microscopy has low sensitivity and culture can take 6 to 8 weeks. Several new methods of diagnosing TB more quickly have been developed including ones based on dipsticks used with urine, and methods based on gene-based tests. The gene-based approaches can help rapid diagnosis of drug resistance. In the geographical areas however where TB is very common many of these new diagnostic tests are not yet available due to weak health systems and poverty.

A significant current and future problem for TB is drug resistance. There is now substantial amount of TB which is resistant to at least one of the key first-line drugs, and a significant and growing problem with multidrug resistant



TB which is resistant to several drugs. There has been good progress in some parts of Eastern Europe and other high-income settings in reducing this, but it is a potentially significant growing problem in Asia, Africa and Latin America.

Tuberculosis vaccination remains based on the old vaccine BCG. It is effective at preventing severe TB in children but it is less effective in adults, less effective in low-income settings and less effective in lung TB. New vaccines have been tried but none so far improved significantly BCG. There is no biological reason to think a better TB vaccine is not possible.

Pulmonary TB is not the only way which tuberculosis can affect the lung. Around 2% is miliary TB which is widely disseminated because the immune system cannot confine it. Untreated mortality from this form is around 100% and even with treatment it can be over 30% in low resource settings. TB can also get into the space between the lung and the chest wall and cause a collection of fluid termed an effusion; this can impair lung function.

The infections above can cause a failure to breathe due to the lung being filled up with pus or fluids or compressed, but if the muscle of the chest wall and diaphragm cease to function people also cannot breathe. Polio, tetanus, botulinum and Guillain-Barre syndrome were considered in the last lecture on the peripheral nerves but one of the principal ways they can kill people is by paralysing the muscles of respiration.

In contrast to some other organ systems the role of parasites in lung disease is relatively modest. One parasite specifically uses the lung as principal home; paragonimus is a fluke which is passed from snails to crabs or crayfish, and if these are eaten uncooked it can cause an infection of the lung which mimics TB clinically. More dangerous, an accidental lung parasite is hydatid disease, the sheep-dog tapeworm. Several worms also pass through the lungs as part of their life-cycle including hookworm and ascaris (roundworm), but generally only cause transitory lung symptoms.

The Heart

Infections can damage the heart through multiple routes. They can settle on and damage the heart valves (endocarditis). They can damage the heart muscle (myocarditis). They can cause changes to the heart rhythm. They can inflame the pericardial sac that surrounds the heart (pericarditis, pericardial effusion) and they can lead to myocardial infarction (heart attack).

Endocarditis of the heart valves is rare but serious; around one in 30,000 get endocarditis. The risk factors are heart structural abnormalities including artificial valves and congenital heart abnormalities; risks for bacteria getting into the blood which include intravenous lines in hospital, intravenous recreational drug use, dentistry and poor dentition, and surgery. Which bacteria causes endocarditis depends on the setting. From hospitals it is usually caused by skin bacteria in particular staphylococcus. Dental and the gut cause endocarditis by different forms of streptococci. Immunosuppressed people can also get fungal endocarditis.

Historically one of the biggest risks for endocarditis, and a major cause of heart damage in itself was rheumatic heart disease. This used to be very common in the UK; chorea which is one of the signs of endocarditis was one of the most common causes for admission at Great Ormond Street Hospital. It is an immunological reaction to Streptococcus A infection with effects throughout the body especially the joints. It damages the mitral heart valve and can cause long term heart failure and the rhythm disturbance atrial fibrillation which is a significant risk factor for stroke. Around 30 million people are thought to be affected by rheumatic heart disease globally but rates are now going down rapidly in most parts of the world. It tends to cluster in urban poorer areas.

Myocarditis, inflammation of the muscle of the heart, is most commonly caused by viruses although a number of bacteria can also cause it. This may be an initial inflammation due to infection, or a more delayed one due to immunological processes. Although most people make a full recovery, it can cause serious heart disease in young adults and children and occasional sudden deaths.



A disease which historically caused a lot of myocarditis was diphtheria; in this case it is caused by the toxin produced by the bacteria. This can in particular cause heart block. Diphtheria is now very rare due to better living conditions, antibiotics and vaccination. A disease which is commoner in certain geographical areas, although decreasing in incidence, largely confined to Latin America, is Chagas disease. This is a parasitic infection affecting the heart passed on by rejuviid bugs. Outside Latin America the tickborne Lyme disease can cause a myocarditis leading to heart block. If treated with antibiotics most people recover in about six weeks but there may be a temporary need for a pacemaker.

The heart is surrounded by the pericardial sac. A few infections, most notably tuberculosis, can cause an effusion of fluid into this space. This can press on the heart and cause it to malfunction. A mild inflammation of the pericardial sac, pericarditis, is quite common following a number of viral infections and causes pain (and ECG changes) that usually recovers uneventfully.

Infections of all sorts can lead to a significantly increased risk of heart attack during, and for some time after the infection. New examples of this are emerging all the time now researchers are looking for it, and for example people hospitalised with pneumococcal pneumonia the incidence of myocardial infarction is 7 to 8%. The indirect effects of infections causing heart attack and stroke, mainly in the elderly, may be more important than the direct effects in many cases.

We are making substantial progress against several major infections of the lungs and heart. There have been rapid reductions in bacterial pneumonia in the very young, a major cause of global mortality. There is a gradual but steady reduction in TB globally although drug resistance is a risk. Many old enemies such as diphtheria and rheumatic heart disease are largely gone, or are clearly going. Pneumonia will however remain a significant risk in the elderly even high-income settings, and heart infections will remain rare but serious hazards.

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