Pneumococcal polysaccharide vaccine in high risk adults

Evidence of efficacy against pneumonia is still limited

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Streptococcus pneumoniae continues to cause a substantial burden of disease and death in adults, despite nearly 100 years of research into disease prevention and the availability of a licensed vaccine. To date, uptake of the vaccine has generally been limited to older adults and those with chronic illness in high income countries. Coverage has been generally suboptimal, perhaps because of the continued controversy about the vaccine's efficacy against various clinical end points and within different populations.

In the linked randomised controlled trial, Maruyama and colleagues assess the effects of the 23-valent pneumococcal polysaccharide vaccine in 1006 nursing home residents in Japan.[1] This is the first trial of this type for many years, and the first to show that this vaccine protects against all cause pneumonia (vaccine efficacy 44.8%, 95% confidence interval 22.4 to 60.8) and pneumococcal pneumonia (vaccine efficacy 63.8%, 32.1 to 80.7) in older adults.

Pneumonia is the most common presentation of pneumococcal disease in adults, and it was outbreaks of pneumococcal pneumonia in otherwise healthy men in barrack accommodation that provided the impetus for vaccine trials in the 1940s.[2] Later trials of vaccines of various valency in South African miners and in Papua New Guinea during the 1970s found reductions in bacteraemic pneumonia, all cause pneumonia, mortality from pneumonia, and all cause mortality (listed in the order of the level of protective efficacy).[3-5] A 14-valent pneumococcal polysaccharide vaccine was subsequently licensed in 1977, then replaced by the higher valency (23-valent) but lower antigen content vaccine in 1983 without additional trials before licensing.[6]

Trials in high income countries after licensing of the 23-valent vaccine have been plagued by problems. Outcomes vary depending on which end point measurement—invasive disease (vaccine serotype or not), presumptive pneumococcal pneumonia, all cause pneumonia, mortality from pneumonia, or all cause mortality—is selected. These measures require large sample sizes if attack rates are low. In older patients and those with chronic illness, randomised controlled trials have failed to find evidence of efficacy against pneumonia or mortality, although these trials were generally underpowered.[7] In addition, the reporting of these later studies was of higher quality than in the earlier studies.[8] Large observational studies have consistently reported vaccine effectiveness against invasive disease in populations in which the vaccine has been used. A recent systematic review shows that for otherwise healthy older adults the vaccine significantly reduced invasive disease but had no effect on other outcomes.[7]

The limitations of Maruyama and colleagues' study make it unlikely that the debate about vaccine efficacy against non-bacteraemic pneumonia in older adults will be quelled. The incidence of pneumonia was high (72.8/1000 person years), and this was not supported by the earlier study that they cite, which did not provide incidence data. The trial was limited by the classification and causes of pneumonia because the authors did not use a standard definition for radiological confirmation. Most cases of pneumococcal pneumonia were diagnosed by urinary antigen, which does not have well defined sensitivity and specificity. However, evidence of a positive effect of vaccination was strengthened by the absence of invasive pneumococcal disease in the intervention group.

The authors claim that the 23-valent vaccine improved survival; however, despite the apparent protective efficacy against all cause pneumonia and pneumonia related mortality (0 in the vaccine group *v* 13 in the control group), this did not translate into a reduction in all cause mortality (even though pneumonia accounted for 26 of 80 (32.5%) deaths in the control group). The overall rate of death did not differ significantly between the vaccine group and the control group.

Existing evidence strongly supports immunising elderly people living in nursing homes. These institutions continue to experience outbreaks of pneumococcal disease with high case fatality rates in poorly vaccinated populations.

The evidence for vaccinating elderly people living at home or those with chronic illness remains contentious. However, the vaccine is safe and probably effective against invasive disease, so clinicians should consider using it in patients who fit these categories.

The greatest burden of pneumococcal disease is in low income countries, and the role of the 23-valent vaccine and other pneumococcal vaccine formulations in these settings needs to be researched. In high income countries, new trials are needed to provide data on preventing pneumococcal disease in high risk adults. However, these studies need to be large and may be too costly. It is unclear whether the conjugate vaccine can overcome the limitations of serotype coverage by providing enhanced protection against disease end points compared with the polysaccharide vaccine. Future research also needs to include better ways to diagnose pneumococcal pneumonia and a standardised definition of radiological pneumonia in adults.

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Sexual activity in middle to later life

Better health leads to frequent, good quality sex in older adults

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A cursory search of the *BMJ*'s archives using the terms "sexuality" and "older adults" yields one study report and one editorial, both published in the past decade.[1 2] Using the terms "sexual activity" and "elderly" yields only two additional citations, which focus on gynaecological and epidemiological topics.[3 4] If for no other reason than that of filling a glaring void, the linked study by Lindau and Gavrilova represents a refreshing addition to the *BMJ*'s sexuality and ageing repertoire.[5] The study is equally refreshing because it offers a health enhancing, health promoting perspective: most human sexuality studies—especially those informing healthcare professionals—centre on outlining problems, diagnosing illnesses, and managing treatments. To unearth positive news amid the rubble of a trouble focused literature is just as refreshing, stimulating, and invigorating as good healthy sex.

Lindau and Gavrilova examined data from two cross sectional surveys of ageing populations in the United States (national survey of midlife development in the United States (MIDUS) and national social life, health and aging project (NSHAP)). They used two representative samples of more than 3000 adults to calculate a "sexually active life expectancy" estimate for men and women in various age groups. Defined as the "average number of years remaining spent as sexually active," this measure represents a "new health expectancy indicator for clinical and public health application." As far as can be determined, Lindau and Gavrilova are the first to propose such a measure. Despite the novelty in content, however, the study presents both good and bad news. The good news highlights prevention: men at age 55 can expect 15 additional years of sexually active life, and women, 10.6 years. The measure helps project and predict the "population structure of sexual activity" and the upcoming "need for public health resources, expertise, and services" and will help address the sexual health of one of the fastest growing demographic groups worldwide.[6]

More importantly, the study bears good news in the form of hope: given the manner in which "second adulthood" has been redefined in recent years, the availability of sexual performance enhancers, the widespread use of the internet for social support, as well as improvements in overall health and better access to care, the news that adults in the US can enjoy many years of sexual activity beyond age 55 is promising.[7 8] In fact, Lindau and Gavrilova document increases in sexual interest among older men in their samples, and a strong association between overall health and sexual partnering and activity in later life for both sexes.

Despite the spotlight this study shines on the sexual health of older adults in the US, less good news lies dormant in the shadows. Take the gender gap in sexually active life expectancy, for instance, which favours men: for men at age 55, sexually active life expectancy was eight to nine years less than demographic life expectancy, whereas for women this difference was 17 to 18 years. Or consider how the new measure provides little detail about the quality of life during these added years. For example, the measure sheds no light on the intriguing—and still poorly understood—question of why, even though they enjoy fewer years of a sexually active life, many women do not perceive this as a "problem."[9] Neither does the measure provide details on how women and men manage, attempt to enhance, or deal meaningfully (and uniquely) with their ageing sexuality. Sadly, even Lindau and Gavrilova attest that, "particularly little has been known about the quality of older women's sexual lives."

Also lying within the shadows of a sexually active life expectancy measure is the great void in what is currently known about older adults outside of the cultural, geographical, economic, and political contexts seen in the US. Researchers and providers have a poor understanding (often misunderstanding) of how cultural and structural factors such as familism (the needs of the family as a group), social class, machismo (male dominance), or marianismo (female dominance) affect the ageing process and sexual health in many of these contexts.[10] Meanwhile, as understanding lags, projections estimate that by 2030 the proportion of people 65 and older worldwide will have grown from 59% to 70%.[6]

Other elements—such as problems with measurement (an old nemesis of sexuality research) and silence regarding the sexual health of ageing homosexual, bisexual, or intersexed people—also linger in the shadows. They stand as dim reminders of the limitations inherent in applying science to the study of complex human

realities, and the cultural values shaping the topics we choose to study.[11]

Thanks to Lindau and Gavrilova we now have a better sense of how much sexually active life lies ahead as we age. How well equipped, willing, and prepared sexuality researchers and healthcare providers are to help foster optimal quality, meaning, agency, and purpose in those added years remains a challenging question for health care and public health.

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Waiting times for radiotherapy after breast cancer

Minimising delay improves outcomes, so investment and planning are needed

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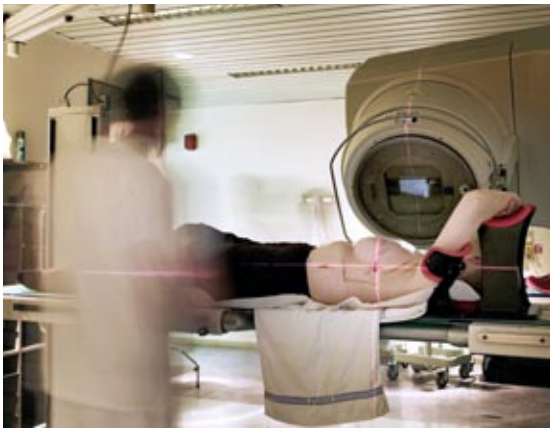
The effect of the time interval between radiotherapy and surgery on the recurrence of breast cancer has been investigated in several countries. Some studies have indicated a positive association,[1 2] whereas others have found no link.[3 4] A recent systematic review concluded that an interval of more than eight to 12 weeks between breast conserving surgery and radiotherapy increased local recurrence rates when no other treatment was given.[5] However, the review summarised studies that had used different cut-off points for time to radiotherapy, which hampers a straightforward interpretation.

In the linked retrospective cohort analysis, Punglia and colleagues assess whether the interval between breast conserving surgery and radiotherapy affects the risk of local recurrence in women with early stage breast cancer in the United States.[6] They found a significantly increased hazard of local recurrence of breast cancer in women who waited more than six weeks for radiotherapy (hazard ratio 1.19, 95% confidence interval 1.01 to 1.39). The association was stronger when the interval was measured as a continuous variable in days, suggesting that a linear association exists between time to radiotherapy and local recurrence. As well as analysing the data using a Cox proportional hazards model that adjusted for other factors, the authors performed propensity score analysis and instrumental variable analysis, both of which produced similar results.

The study found only a modest effect, and it could still be explained by residual confounding. Some important factors such as radiation dose were not available in the analysis and thus could not be accounted for. Several clinical factors were significantly associated with receipt of early radiotherapy. Women with nodal involvement and greater comorbidity were more likely to have radiotherapy after six weeks. Thus, the timing of radiotherapy does not seem to be entirely dependent on available capacity at the treatment centre. Selection mechanisms involving important confounders may bias observational studies such as this, and concerns have been raised about the effectiveness of propensity score analysis and instrumental variable analysis in tackling confounding by indication.[7]

However, even if some doubt exists about the cause and the strength of the association, delays in radiotherapy cannot be accepted for several reasons. Firstly, the results may reflect a real biological effect so should be taken seriously. Secondly, increased waiting times for treatment are highly likely to lead to stress and anxiety for patients, although qualitative studies are needed to confirm this. Furthermore, Punglia and colleagues found that black and Hispanic women, and those with a "personal history of low income," were more likely to receive their radiotherapy more than six weeks after surgery.[6] They also found a geographical difference, with women who lived in the southern states of the US more likely to have radiotherapy within six weeks. These patterns were still apparent when the analyses were adjusted for year of diagnosis and other clinical factors. Similar findings have been reported in the United Kingdom: in England an audit examined data on all patients with cancer undergoing radiotherapy in a single week in 2007.[8] The audit showed that patients with cancer were less likely to receive radiotherapy if they lived in more deprived areas.



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Healthcare providers therefore need to assess where potential delays are occurring and ensure that they are reduced, as well as ensuring equal opportunities in accessing good care. In the UK, this process should be easier than in many other places because planning and treatment are done within a single organisation—the NHS. Reorganising the planning and logistics of radiotherapy to reduce waiting times will probably require extra investment. If substantial investment would be needed because lack of resources is the reason for long waiting times, the modest effects seen in this study would have to be weighed against other opportunities and priorities in cancer care. The use of multidisciplinary teams also improves the continuity and coordination of a patient's care.

One good example of how practices can be improved is the Rapid Response Radiotherapy programme in Ontario. This programme has drastically shortened waiting times for patients having palliative radiotherapy by restructuring the referral process so that many patients are treated on the same day as their consultation.[9] Countries where disconnected systems are responsible for different aspects of treatment will find it more difficult to ensure that diagnosis, referral, and treatment are not subject to delay.

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Tiotropium and chronic obstructive pulmonary disease

A good foundation therapy for most patients

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Tiotropium is a once daily, inhaled, long acting anticholinergic drug that provides at least 24 hour improvement in airflow and hyperinflation in patients with chronic obstructive pulmonary disease (COPD). Clinical trials have consistently shown that these physiological effects translate into improvements in lung function, exercise tolerance, and health related quality of life, in addition to fewer exacerbations.[1]

Many national and international guidelines suggest using either a long acting β2 agonist or long acting anticholinergic to treat COPD, but because both are effective and convenient no guidance has been given on which one to choose if short acting agents fail to improve dyspnoea.[2]

Over the past two decades, the short acting anticholinergic, ipratropium, has been widely prescribed for maintenance treatment, at two inhalations of 20 µg four times a day via a metered dose inhaler. This dosage has also been used as the standard comparison in registration clinical trials. However, this dosage is not ideal, and most doctors commonly prescribe much higher doses in an attempt to improve efficacy. Yet boosting the dosage cannot overcome the short lived activity of ipratropium. Alternatively, a once daily long acting anticholinergic improves outcomes more than the standard dose of a short acting anticholinergic or a combination of ipratropium and salbutamol (short acting anticholinergic and short acting β2 agonist).[3]

Use of inhalers is not intuitive, so all patients need careful instruction, particularly if they are using a metered dose inhaler. Indeed, a common reason for lack of improvement of patients' symptoms is poor inhaler technique and adherence. Dry powder inhalers are usually simpler to use, but the correct technique still needs to be carefully taught to the patient and checked at each visit.

The long acting anticholinergic, tiotropium, is most commonly delivered via the HandiHaler dry powder inhaler (18 µg/day) and more recently in some countries by a new propellant-free delivery system called the Respimat soft mist inhaler (2.5 µg two inhalations once a day). This last system is an effective alternative multi-dose delivery device for tiotropium.[4]

However, despite the widespread use of tiotropium and other anticholinergics in COPD over the years, two recent publications—a nested case-control study and a systematic review with meta-analysis[5 6]—have introduced uncertainty about the safety of these drugs. The studies reported an increased risk of all cause mortality and mortality from cardiovascular disease, myocardial infarction, and stroke in patients with COPD who received either tiotropium or short acting inhaled anticholinergics.

Thankfully this uncertainty has been promptly and adequately tackled by updating the clinical trial safety database for tiotropium, principally by adding data from the four year UPLIFT trial.[7] The resulting database includes 30 trials in which 10 846 patients were randomised to tiotropium and 8699 to placebo. An analysis of these trials indicated that tiotropium was associated with a reduction in the risk of all cause mortality, mortality from cardiovascular disease, and cardiovascular events.[8]

Undoubtedly, the alternative choice of a long acting β2 agonist (salmeterol or formoterol) will also improve lung

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function in COPD. Monotherapy with a long acting β2 agonist must be avoided, however, if the clinical suspicion of COPD has not been confirmed by spirometry, because of the risk of increased mortality in undiagnosed asthma masquerading as COPD.[9] In practice, many doctors avoid this by early introduction of treatment with an inhaled corticosteroid plus a long acting β2 agonist. However, this "asthma"-like approach is costly and puts patients at risk of the well known complications of inhaled steroids and pneumonia—which is specific to people with COPD.[10]

Screening spirometry is being advocated and adopted to increase the diagnosis of COPD.[11] It helps identify patients with milder disease, for whom aggressive modification of risk factors can be successful. Recent subgroup analyses of the major COPD trials TORCH and UPLIFT have highlighted the importance earlier treatment.[7 10]

Primary care doctors need to reduce the risk of symptoms worsening after patients stop smoking, identify patients with COPD early, and support them in managing symptoms in accordance with current guidelines. Educating and vaccinating patients (annual influenza vaccination along with pneumococcal vaccination (at least once)), encouraging them to exercise, and introducing foundation therapy are appropriate goals for primary care doctors. Patients who do not respond to such an approach may need to be referred to a local COPD clinic for further investigation and individualised care.

Current guidelines favour a stepwise approach to pharmacotherapy.[2] All patients should have a rescue short acting β agonist to prevent or reduce acute symptoms, along with tiotropium as initial maintenance or foundation treatment. This could be complemented by a long acting β2 agonist in patients with persistent dyspnoea (emphysema), and by a combination of drugs in those with frequent or recurrent exacerbations (chronic bronchitis).[2] New drugs such as phosphodiesterase type-4 inhibitors may play an important role in patients with infrequent exacerbations before turning to a combination of inhaled corticosteroid and long acting β2 agonist.[12]

Tiotropium is not the "holy grail" of treatment for COPD because it does not slow the loss of lung function,[9] but it does improve many patient centred outcomes. This supports its adoption as a safe and effective foundation treatment for all patients except those with mild COPD who need only an occasional short acting β2 agonist to be taken when needed.

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Doctors and assisted suicide

New policy fulfils a legal requirement, but the implications are unclear

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After the litigation relating to Debbie Purdy,[1] a woman with multiple sclerosis who successfully argued for the right to know the grounds on which a decision to prosecute someone for assisting a suicide is made, the director of public prosecutions published guidance this February on the prosecution policy relating to charges brought under the Suicide Act 1961 in England and Wales.[2] The policy, which lists factors for and against prosecution, was devised after a public consultation exercise, where almost 5000 respondents commented on the interim guidance published in September 2009.[3 4] As expected, the director of public prosecutions made changes in the final policy.[5]

What may have come as a surprise is the apparently heightened risk of prosecution that doctors now face under the Suicide Act.[6] The guidance states that there will be, prima facie, a greater public interest in prosecuting a suspect who assists or encourages a suicide when "acting in his or her capacity as a medical doctor . . . [when] the victim was in his or her care."[2] The director of public prosecutions suggests that the likelihood of prosecutions

Public interest factors affecting the decision over prosecution with potential relevance for doctors

Factors tending in favour of prosecution

- The victim was under 18 years of age
- The victim did not have the capacity (as defined in the Mental Capacity Act 2005) to reach an informed decision to commit suicide
- The suspect gave encouragement or assistance to more than one victim, and these victims were not known to each other
- The suspect was acting in his or her capacity as a medical doctor, nurse, other healthcare professional, a professional carer, or as a person in authority, such as a prison officer, and the victim was in his or her care

Factors tending against prosecution

- The victim had reached a voluntary, clear, settled, and informed decision to commit suicide
- The actions of the suspect, although sufficient to come within the definition of the offence, were of only minor encouragement or assistance
- The suspect had sought to dissuade the victim from taking the course of action that resulted in his or her suicide
- The actions of the suspect may be characterised as reluctant encouragement or assistance in the face of a determined wish on the part of the victim to commit suicide

The full list runs to 16 factors in favour of prosecution, and six against[2]

remains unaffected,[7] but there may be some scepticism about this, especially among specific groups explicitly noted in the guidance. If after the public consultation the director of public prosecutions has become persuaded of the particular relevance of a doctor's involvement in assisted suicide, then surely that factor's presence will bear on the prosecutor's discretion, even if it does not finally settle a decision to prosecute.

Doctors and patients may be concerned about how to interpret the guidance. Strictly speaking, however, it is not aimed at them but at the Crown Prosecution Service,[4] and if a patient seeks assisted suicide, the best (legal) advice for doctors worried that they may risk breaking the law is to consult their defence organisation.[6] Nevertheless, official guidance on the law and policy is welcome. The director of public prosecutions' earlier approach to the problem has been described as "combining a strict interpretation of the Suicide Act for the evidential test, with a liberal interpretation of public interest."[8] This perspective endures after the implementation of the new guidance and the recent amendments to the Suicide Act. For evidentiary purposes, the guidance provides a wide threshold for suspects' participation, saying, "A person commits an offence under section 2 of the Suicide Act 1961 if he or she does an act capable of encouraging or assisting the suicide or attempted suicide of another person, and that act was intended to encourage or assist suicide or an attempt at suicide."[2]

In this context, the intention to encourage or assist may incorporate foresight of a virtual certainty, rather than simple desire or purpose[9 10]: foreseeing the virtual certainty of a result (such as a suicide attempt) can allow for a finding of intention, even when that result is not something a person would have wanted or sought to bring about. Thus, many acts of assistance may satisfy the active aspect of the offence, including some that relate to suicides that take place in other jurisdictions. But even when it is beyond doubt that there has been assistance or encouragement, the prosecutor is not obliged to prosecute. The question about public interest remains and is influenced by the guiding prosecutorial factors.

The director of public prosecutions lists 16 factors that tend in favour of prosecution, such as the victim being a minor, lacking decision making capacity, or making the decision involuntarily (box). The general conduct of the suspect is also relevant—for example, encouraging or assisting more than one victim and assisting or encouraging when acting in the capacity of a healthcare professional also weigh in favour of prosecution.

Six factors militate against prosecution. These include the suspect's actions only providing "minor encouragement or assistance," the suspect having sought to dissuade the victim from committing suicide, and reluctant assistance on the suspect's part in the face of a determined wish of the victim to commit suicide.[2] Two points that contrast with the interim policy are noteworthy. Firstly, a victim's medical condition—be it chronic, debilitating, or terminal—will not presumptively bear on the public interest issue. Secondly, a ranking of "weightier" and "less weighty" factors no longer exists.[5]

Although presumably satisfying his legal obligation to publish the policy, the director of public prosecutions claims that the factors listed in the policy are not exhaustive: each case will be decided on its merits. So, how much greater certainty does it provide for doctors who are concerned about difficult discussions with their patients? It seems not much. However, in times where evidence bases seem to count for a lot, it may be worth noting that although the relative risk of prosecution for doctors may have increased with the new policy, the absolute risk was very low in the beginning. Huxtable thoroughly reviewed prosecutions of medical participation in killings and concluded, "an accusation is not impossible to countenance, but a conviction is currently highly improbable."[11]

1 R (on the application of Purdy) *v* DPP [2009] UKHL 45.
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3 Director of Public Prosecutions. Interim policy for prosecutors in respect of cases of encouraging or assisting suicide. 2009. Crown Prosecution Service. www.cps.gov.uk/consultations/as_policy.pdf.
4 Huxtable R, Forbes K. New interim guidance on assisted suicide. *BMJ* 2009;339:1209-10.
5 Director of Public Prosecutions. Public consultation exercise on the interim policy for prosecutors in respect of cases of assisted suicide—summary of responses. 2010. Crown Prosecution Service. www.cps.gov.uk/consultations/as_responses.html.
6 Dyer C. Doctors face greater risk of prosecution than close relatives or friends for assisting a suicide. *BMJ* 2010;340:497.
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10 Huxtable R. The suicide tourist trap: compromise across boundaries. *J Bioeth Inq* 2009;6:327-36.
11 Huxtable R. *Euthanasia, ethics and the law: from conflict to compromise*. Routledge-Cavendish, 2007.