

Staples for skin closure in surgery

Are quicker than sutures, but may increase complications



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B I Singh consultant orthopaedic surgeon, Medway Foundation NHS Trust, Gillingham ME7 5NY
C Mcgarvey specialist registrar, trauma and orthopaedics, Medway Foundation NHS Trust, Gillingham ME7 5NY

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About 230 million major surgical procedures are performed worldwide each year,¹ and morbidity and mortality after surgery vary widely. Three recent publications highlight the long term implications of surgical complications, both for 30 day survival and “sickness absence.”¹⁻³ In the linked systematic review, Smith and colleagues assess clinical outcomes using staples compared with sutures in wound closure in orthopaedic surgery.⁴

Postoperative infection is a major source of morbidity, mortality, and hospital costs, but it is not completely avoidable because certain factors—such as age, drugs, systemic illness, and type of surgery—cannot be changed. Interventions to reduce infection, such as the use of perioperative antibiotics and clean air operating theatres, are well established. The literature is sparse, however, on the role of skin closure technique on the rates of infection.

Wound closure creates the tensile strength that holds the wound edges together and it provides an effective seal until healing takes over. Effective wound healing minimises infection and produces a satisfactory cosmetic result. In orthopaedic surgery, superficial infection can be associated with increased risk of deep infection and reduced implant survival.

The preferred method of skin closure varies within and across all branches of surgery. The skin can be closed by continuous subcuticular sutures, interrupted sutures, or skin staples. Data are also now available that compare adhesive and more established techniques.⁵

Smith and colleagues report the first meta-analysis comparing sutures and staples in orthopaedic wounds. Data from six studies, three of which were randomised, and 683 orthopaedic procedures showed that the risk of infection was three times higher when staples were used (relative risk 3.83, 95% confidence interval 1.38 to 10.68).⁴ When hip procedures were looked at exclusively, the risk of infection was four times greater when staples were used (relative risk 4.79, 1.24 to 18.47). However, no difference was seen in infection rates when staples were used for total knee replacement.⁴

Smith and colleagues' data fit with evidence from other specialties. Three of five randomised controlled trials that compared the use of sutures with staples in the closure of chest and leg wounds in cardiothoracic surgery found a lower complication rate with sutures, and all trials found that sutures produced a better cosmetic result.⁶ One systematic review compared the use of sutures and staples after elective caesarean section. It found that staples were quicker, but postoperative control of pain was better after sutures. No significant difference was seen in cosmetic appearance or infection rate at six weeks.⁵ Abdominal wounds closed with sutures have been associated with increased postopera-

tive pain and poorer cosmetic outcomes, but no difference in complications.⁷ Several studies have shown that using staples to treat scalp lacerations in the emergency department is faster, less expensive, and not associated with an increased rate of complications.⁸

The most consistent benefit of staples is more rapid skin closure, yet the time saved is rarely more than two to three minutes.⁹ Although theatre time is estimated at £5 (€5.7; \$8) to £15 a minute, this represents a relatively small proportion of the total time spent by patients in theatres or operating departments. Secondly, the saving may be reduced by the increased costs of removing the staples (compared with absorbable subcuticular stitches) and reduced even further by the costs of treating the increased number of infections. Studies in orthopaedic and cardiothoracic surgery attribute a higher cost to the use of staples.¹⁰

Smith and colleagues acknowledge that only one of the five papers studied in their analysis was appropriately designed and reported. Three studies were randomised but only two studies were adequately blinded, and risk factors for poor wound healing such as steroid use and diabetes were not documented. Furthermore, the observed increase in infection rate seems to have been influenced mainly by the difference in outcomes after hip fractures. Of the four studies of hip surgery, two exclusively included people with hip fracture, who may be more vulnerable to wound infection. Furthermore, because of the lack of random concealed allocation, the most vulnerable of these people may have been allocated staples to minimise time under anaesthesia.

Well designed randomised controlled trials are needed to examine further the increased risk of infection risk found by Smith and colleagues. They are also needed to discern whether the risks are exclusive to hip surgery, and to compare the risk of infection with staples in elective hip arthroplasty as opposed to hip fracture. We now have national databases of the outcome of hip and knee arthroplasty and hip fracture, but currently neither records the method of skin closure. These databases could provide the platform to enable comprehensive adequately powered studies.

The *Medical Journal of Australia* has recently updated its guidelines for skin closure in the treatment of hip fractures, and they state that superficial wound complication rates are higher for wounds closed with metallic staples than for wounds closed with subcuticular vicryl.¹¹ The British Orthopaedic Association's “blue book” for best practice in fragility fractures states that no strong evidence exists to support or condemn the use of either sutures or staples, but that patients should be made aware of which will be used.¹² On the best available evidence, it may be more difficult to justify the use of staples in these patients.

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BCG vaccination in developing countries

Important interactions occur with other vaccines, vitamin A, and the organisms that cause fatal pneumonia



JENNY MATTHEWS/PANOS

BCG vaccine is given to more than 100 million infants each year, making it one of the most widely used vaccines.¹ In the linked randomised controlled trial, Roth and colleagues assess whether revaccinating children at 19 months reduces overall child mortality.²

A single dose of BCG provides useful protection against systemic mycobacterial infections, such as tuberculous meningitis, miliary tuberculosis, and leprosy.^{1,3} It is less effective against pulmonary tuberculosis—effectiveness varies greatly between trials, but geographical latitude and study validity explained 66% of this variance in one meta-analysis.⁴ BCG was less effective near the equator, in lower quality trials, and in rural areas, but effectiveness was not influenced by age at vaccination or the strain of BCG used.^{4,5} BCG may be of less benefit to people living in tropical or rural areas because they have greater contact with environmental mycobacteria. These organisms may have heterologous (non-specific) immunological effects that provide some protection against tuberculosis but also reduce the effectiveness of BCG.⁵

Because BCG provides useful protection against tuberculous meningitis and miliary tuberculosis in children, the World Health Organization recommends that it be given as soon as possible after birth to all infants living in areas where tuberculosis is highly endemic.¹ WHO also recommends that BCG be given only once, largely because of the lack of evidence that revaccination is beneficial.^{2,3,6-8} Two randomised controlled trials, a case-control study, and a cohort study have suggested that revaccination with BCG does not reduce the incidence of pulmonary tuberculosis.^{3,6-8} However, all these studies were performed in countries near the equator, where BCG is likely to have little effect on pulmonary tuberculosis.⁵ The two randomised trials and the case-control study were confined to people with at least one BCG scar, so we do not know whether a second dose of BCG is helpful in people with no scar, although the presence of a scar and the reaction to purified protein derivative are probably not a reliable guide to immunity to tuberculosis.⁶

Revaccination with BCG may still be beneficial even if it does not provide extra protection against pulmonary

tuberculosis. Attenuated *Mycobacterium bovis* (BCG) has potent heterologous effects on the immune response to many organisms other than *M tuberculosis*, including other mycobacteria (*M avium intracellulare*, *M leprae*, *M microti*, *M ulcerans*), other bacteria (*Brucella*, *Coxiella*, *Listeria*, *Salmonella*), protozoa (*Babesia*, *Leishmania*, *Plasmodium*, *Toxoplasma*), and vaccinia virus.⁹ These heterologous effects have an important influence on human infections other than tuberculosis. Randomised trials of a single dose of BCG in the United States and the United Kingdom published in the 1940s and 1950s showed that it substantially reduced mortality even after excluding deaths from tuberculosis and accidents.¹⁰

Two randomised trials have shown that revaccination with BCG provides protection against non-tuberculous infections.^{3,11} One trial of 121 020 people in Malawi showed that revaccination increased protection against leprosy by about 50% compared with a single BCG vaccination, even though it did not protect against pulmonary tuberculosis.³ In the other trial, 41 302 children born in Algeria between 1935 and 1947 were given BCG orally at birth and then alternately allocated to receive no further doses or three extra doses at 1, 3, and 7 years of age; revaccination reduced total mortality between 1 and 11 years of age by 27% (95% confidence interval 22% to 31%).^{2,11}

Although BCG reduces mortality from diseases other than tuberculosis, diphtheria-tetanus-pertussis (DTP) vaccine may increase mortality from infections other than diphtheria, tetanus, and pertussis in some circumstances.^{2,12} To assess whether BCG can counteract these harmful non-specific effects of DTP, Roth and colleagues randomised children to receive either no vaccine or a second dose of BCG at 19 months of age, one month after they should have received a booster dose of DTP (DTP4).² All the children had been given BCG in infancy. No significant difference in mortality was seen between the groups (hazard ratio 1.20, 0.77 to 1.89).

Unfortunately, the trial was inconclusive for several reasons. Firstly, as discussed in the paper, monitoring of the progress of the trial was not ideal. Secondly, mortality during the trial was lower than expected, which is a common

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Frank Shann professor of critical care medicine, Intensive Care Unit, Royal Children's Hospital, Parkville, VIC 3052, Australia shannf@netspace.net.au

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finding when free medical care is provided during a study in an area with high mortality. Thirdly, and most importantly, major interactions occurred between BCG, vitamin A, and DTP. Sixty per cent of the children had not received the DTP4 booster at the time of enrolment, and importantly many of these children were given DTP after they had been vaccinated with BCG at 19 months of age. Children who received BCG had a lower mortality than the controls if they had received DTP4 before enrolment (hazard ratio 0.36, 0.13 to 0.99) and a higher mortality if they had not received DTP4 before enrolment (hazard ratio 1.78, 1.04 to 3.04). Mortality was 0.36 per 100 person years if DTP4 had been given before BCG revaccination, 1.02 in controls who were not revaccinated with BCG (mortality was not affected by DTP4 status at enrolment), and 1.83 if DTP4 had not been given before BCG revaccination. These findings suggest that it may be beneficial to give BCG after a booster dose of DTP, but that it may be harmful to revaccinate with BCG if this is followed by a dose of DTP. Children were not randomised to receive DTP4 before or after BCG revaccination in this study, so the apparent interaction between DTP and BCG may have been the result of confounding, although this seems unlikely. Similar positive and negative heterologous interactions are common in the immunological literature.¹²

The study adds to the existing evidence that BCG, DTP, and measles vaccines have important heterologous interactions with each other as well as with the pathogens that cause fatal pneumonia in children in developing countries, and that the order in which vaccines are given is important.^{2,12} This raises the exciting prospect that we

may be able to reduce child mortality substantially by revising the current immunisation schedule, and it suggests that new vaccines should be tested for their effects on total mortality and not just their effects on the target diseases.

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Critical illness as a result of influenza A/H1N1 infection in pregnancy

Mortality is high, but lower than expected



ALPHOTO/SPL

The 2009 pandemic influenza A/H1N1 virus has a predilection for the lower respiratory tract. In some cases, infection results in a pneumonitis and severe acute respiratory distress syndrome, which can be difficult to manage despite advanced ventilatory techniques. The effects of H1N1 infection on pregnant women became cause for concern early in the course of the current pandemic because of initial experience¹ and data from previous pandemics.²⁻⁴ In the linked study, the ANZIC influenza investigators provide a detailed analysis of a cohort of pregnant women who developed critical illness as a result of pandemic H1N1 infection in 2009.⁵

During pregnancy changes occur to a woman's immune system to facilitate tolerance of paternally derived fetal antigens. While the pregnancy is recognised by the maternal immune system, the immune response is characterised by an altered TH1-TH2 (type 1-type 2 T helper cell) balance. The maternal immune response favours humoral immunity (TH2 response), and suppresses cell mediated immunity (TH1 response), which could be harmful to the fetus.⁶ This altered immune response may predispose pregnant women

to increased severity of certain infections, including viral pneumonitis. Pregnant women have an increased risk of being admitted to hospital for pulmonary complications of seasonal flu, and the risk increases during later stages of gestation and with associated comorbidity,⁷ but flu related maternal mortality outside of a pandemic is low. In contrast, in previous flu pandemics, maternal mortality has been higher than that seen in the non-pregnant general population. During the 1918-9 pandemic, maternal mortality was reported to be 27% in a review of 1350 cases,² and as high as 50% in an indigent population.³ In the 1957-8 epidemic, half of the women of child bearing age who died were pregnant.⁴

Public health agencies in the United States reported outcomes of pregnant patients with 2009 H1N1 infection from early on in the pandemic. An initial report in May 2009 from the Centers for Disease Control and Prevention (CDC) described 13 cases; three of these women were admitted to hospital, and one died.¹ A more detailed report from the CDC published in August 2009 described 34 cases; six of these women died, and the hospital admission rate was

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Stephen E Lapinsky associate professor of medicine, Interdepartmental Division of Critical Care, University of Toronto, Toronto, ON, Canada
stephen.lapinsky@utoronto.ca

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Tom Nolan describes a tale of two summits in his *BMJ* blog about the Royal College of General Practitioners meeting on pandemic flu at blogs.bmj.com/bmj/category/flu-pandemic-updates/

For links to more *BMJ* Group articles on pandemic flu, visit pandemicflu.bmj.com

estimated to be four times higher than that of the general population.⁸ A study from California that described 102 obstetric patients found that mortality was 8%, and it showed that early antiviral therapy improved the outcome.⁹ Compared with the usual maternal mortality from all causes in the United Kingdom of less than 100 women per year (0.014% of pregnancies), maternal mortality from H1N1 infection is strikingly high.¹⁰

The Australian and New Zealand Intensive Care (ANZIC) Influenza Study Investigators carried out a detailed inception cohort study of all critically ill patients in Australia and New Zealand with 2009 H1N1 infection,¹¹ and also specifically looked at the pregnant and postpartum subgroup.⁵ Sixty four pregnant woman were admitted to intensive care for H1N1 infection in Australia and New Zealand between 1 June and 31 August 2009. This was around a seven times higher risk of admission compared with non-pregnant women of childbearing age. Forty four (69%) pregnant women admitted to intensive care needed mechanical ventilatory support, and nine women (14%) received extracorporeal membrane oxygenation.

The linked population based cohort study provides detailed data to enhance our understanding of maternal risk as well as maternal and neonatal outcomes. Outcomes are better than in previous pandemics, but the results are still worrying. Mortality for these critically ill pregnant women was 11% (33% for those requiring extracorporeal membrane oxygenation) and fetal loss was 12%. Although this is a high figure for young pregnant women, it is a good outcome for a cohort of patients with severe acute respiratory distress syndrome. The study also confirmed that previously reported risk factors for severe disease—including indigenous population status, presence of comorbidity, and obesity—are associated with a worse outcome.

Pregnant women, particularly those in the second half of their pregnancy, have a greatly increased risk of developing severe pneumonitis associated with pandemic H1N1. Despite evidence of an increase in maternal mortality after infection with H1N1, in the later phases of the pandemic its effect on pregnant women has been less than was initially anticipated. This may be attributable to worldwide recommendations for pregnant women to be vaccinated against the 2009 H1N1 strain and advice to facilitate early access to antiviral treatment for pregnant women with symptoms of flu.¹²

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Passive smoking and children

Full protection is needed urgently

On 24 March, the tobacco advisory group of the Royal College of Physicians (RCP) in England published its report on passive smoking and children. The report details the effects of exposure to secondhand smoke in children and includes a chapter on associated costs, a consideration of ethical problems, and a review of potential strategies to tackle the problem.¹

The report attests to the substantial expansion of research on the health effects of passive smoking and the measurement of harmful exposure.¹ We now know that no level of exposure is safe; that exposure to passive smoke in childhood is strongly associated with a range of respiratory effects and serious diseases, including sudden infant death syndrome; and that exposure is a likely cause of brain tumours, leukaemia, and meningitis in children.^{1–3} However, the report excludes established late effects of in utero, childhood, and adolescent exposure including reductions in the fertility of female offspring,⁴ and breast cancer in premenopausal adult women.^{2,5} In fact, evidence is mounting that non-smokers exposed as children are at risk of a range of adult onset diseases.

With increasingly comprehensive restrictions in public spaces, both indoors and out, we are beginning to tackle protection in children's home environments—homes, multi-unit dwellings, and family vehicles. The arguments for increasing protection for children in these spaces are strong. The home is the major source of exposure, children are more vulnerable than adults, and restrictions in homes reduce the likelihood that adolescents will start to smoke and progress to regular smoking.⁶

Smoking in enclosed spaces persists over time, and the hazard increases when nicotine residues react with ambient nitrous acid, found indoors and in vehicles, to form potent carcinogens.⁷ Heavy metals, such as cadmium and lead, are also deposited on furniture, carpets, and clothing, so infants and children continue to be exposed when active smoking has ceased.⁸ Limiting smoking to outdoors can reduce indoor exposure considerably, but outdoor exposures can be substantial,⁹ and residues are carried back inside on hands and clothing.

Roberta Ferrence executive director, Ontario Tobacco Research Unit, Dalla Lana School of Public Health, University of Toronto, 33 Russell St, Toronto, Canada M5S 2S1
roberta_ferrence@camh.net

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KUTTING - PEOPLE / ALAMY

Smoking in multi-unit dwellings is increasingly under threat as non-smoking tenants demand smoke-free environments and landlords become aware of the business case for smoke-free buildings. Bans on smoking in publicly funded multi-unit housing are planned or implemented in several communities.

Many jurisdictions now ban smoking in family vehicles when children are present. However, even with these restrictions, children still face harmful exposures if adults continue to smoke inside the vehicle when they are not there.¹⁰ Current and proposed legislation could easily be expanded to eliminate all smoking in family vehicles, offering improved protection for everyone.

The RCP report recommends a range of effective general population strategies to protect children by reducing smoking among adults—pricing strategies, reduction of contraband cigarettes, mass media campaigns, and enhanced cessation services¹—but more direct measures will be needed to speed the process.

We now have major inconsistencies in our approach to protecting children from passive smoke. It is acceptable to ban smoking in some home environments, such as family vehicles, multi-unit dwellings, and child protection and custody settings, but providing legal protection for children in detached homes and intact families is not viewed as “an effective or ethically justifiable approach”; moreover, “legislation . . . would be difficult to design, implement and enforce.”¹¹ Yet, legal bans have broad public support; in Ontario, Canada, for example, 78% of adults surveyed in 2008 expressed support for bans on smoking in homes with children.¹¹

There are other examples of laws that set a social norm for behaviour. At least 25 countries have introduced a full ban on corporal punishment for children.¹² In Sweden, there are no legal penalties for spanking children, and most who violate the law are referred for counselling. A similar approach could be used for passive smoke.

In some jurisdictions, existing legislation could be used to compel adults to smoke outdoors and thereby reduce exposure in their children. In Ontario, Canada, for example, the Child and Family Services Act (1990) requires that health professionals report children at risk of harm. While this legislation is not widely used for protection from sec-

ondhand smoke, it could be employed in cases of acute risk from asthma or other respiratory diseases.

Another concern is the liability of adults who continue to expose children to passive smoke. Will children who become sick from such exposure seek compensation from their parents or from government for failing to protect their health when we have solid evidence for serious health effects? Do doctors and other healthcare professionals not have a duty to advise their patients to protect their children from passive smoke?

A decade from now, exposing children to passive smoke will probably be unthinkable in most quarters. Public discussion about the ethical and legal considerations of child protection from passive smoke is urgently needed, along with workable measures to protect our most vulnerable citizens. Children should not be the last to be protected from this major cause of death and disease.

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Over the counter chloramphenicol eye drops

The biggest concern is not resistance, but ineffectiveness



STEVEN MAY/LAWRY

Geoff Scott consultant microbiologist, University College London Hospitals, Windeyer Institute, London W1T 4JF

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After much agonising, in 2005 the Medicines and Healthcare Regulatory Agency (MHRA) in the United Kingdom decided to allow pharmacists to dispense chloramphenicol eye drops and ointment without a doctor's prescription. Pharmacists used to be able to sell "Golden Eye Ointment," which contained a sulphonamide, until the sulphonamide component was withdrawn some years ago by the Committee on Safety of Medicines because its clinical activity had not been proved. Chloramphenicol preparations retail at £5.50 (€6.3; \$8.5) to £6 each, a little less than the current cost of a prescription.

A recent study shows that the number of units of chloramphenicol eye drops dispensed between 2004 and 2007 increased dramatically, from 2.3 million to 3.4 million a year.¹ This rise of 48% coincided with a fall in medical prescriptions of 16%. Might this have led to an increase of resistance in common flora that can cause invasive disease, and if so, does it matter? Eye preparations pass down the nasolacrimal duct, where they will encounter *Staphylococcus aureus*, and further back into the nasopharynx, where they will meet *Streptococcus pneumoniae* and *Haemophilus influenzae*. Chloramphenicol will also be swallowed so that gut flora may be exposed to very low concentrations of the antibiotic.

In the UK, the widespread use of systemic chloramphenicol gradually faded during the 1980s to be replaced by cephalosporins, quinolones, and macrolides as first line agents in the management of, for example, invasive infections of the lung and central nervous system and enteric fever. Resistance to chloramphenicol in imported *Salmonella typhi* and *S paratyphi* is relatively common, but chloramphenicol is probably slightly less active than quinolones and azithromycin even against sensitive strains of these organisms. So very little of this antibiotic is used systemically in the UK now. Nevertheless, perpetuation of chloramphenicol resistance in—for example, *Escherichia coli* in the urine—results from genes that encode chloramphenicol resistance being linked on plasmids or integrons to those that encode resistance to trimethoprim.

Bacteria do not have simple mechanisms of mutation to resistance to chloramphenicol but have to acquire "new" genetic information. Resistance is generally mediated by the gene encoding chloramphenicol acetyl transferase (*catA*), which is usually borne on a plasmid. This gene may also be included in integrons containing several resistance genes, which can also be transferred from one bacteria to another. Other possible mechanisms include change in permeability of bacteria or even active export of chloramphenicol, genes for which could be upregulated by exposure to the drug.²

It is difficult to measure antimicrobial resistance in any meaningful way. Clinical isolates are by their very nature highly selected and do not reflect changes in normal flora. Changes in resistance to chloramphenicol in clinical isolates are unlikely to be noticed in the UK because the drug is rarely prescribed. In many laboratories, isolates may not even be tested. Prospective microbiological studies of

normal nasal and pharyngeal flora before and after using chloramphenicol would indicate the true risk of selecting resistance but would not be funded.

Specimens for culture and virology are rarely received in the laboratory given the large number of patients with transient conjunctivitis. And neither would pharmacists have the inclination or ability to send such specimens to the laboratory. Furthermore, a recent randomised trial in 326 children found that chloramphenicol is no better than placebo in terms of clinical cure at seven days (83% in those taking placebo and 86% in those taking chloramphenicol; risk difference 3.8%, 95% CI -4% to 12%).³ The reason for the failure of topical chloramphenicol in this acute bacterial infection is not clear—most infections are associated with susceptible virulent bacteria, and the recoverable bacterial load does fall with chloramphenicol treatment. Perhaps it is because the drug fails to get to where the bacteria are dividing. It is more likely, however, that the inflammatory process is self limiting, and that killing the bacteria has no effect on this process. The relatively few cases of viral (for example, adenovirus) infection would not be expected to respond anyway.

Oral chloramphenicol, although cheap to make and used extensively worldwide, is now expensive in the UK—it is one of the most expensive antimicrobials in the formulary—so it is unlikely to be used extensively in the foreseeable future. Intravenous chloramphenicol is still useful for managing occasional intracranial infections or ventilator associated pneumonia caused by coliforms and staphylococci that are resistant to other antibiotics. Chloramphenicol is also used in certain practices in agriculture, such as the farming of prawns.

The MHRA made an error in allowing the sale of chloramphenicol, not because of the dangers of unwanted effects or of selecting for resistance, which are minimal, but because the treatment is ineffective. Soothing eye preparations are all that is needed, and people who do not respond to this management after about three days should see a doctor to have specimens taken so that appropriate treatment can be given.

The prescription of antibiotics by non-medically qualified personnel raises strong bipolar opinions. Some people thought that this move was the thin end of an unacceptable wedge, and that pharmacists would soon be able to sell common oral antibiotics without prescription. Ideally, that would lead to a reduction in overall use of antibiotics, but the case of chloramphenicol eye drops suggests that an increase would be more likely.

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