Supply of benzathine penicillin G: the 20-year experience in Australia

Rosemary Wyber,1 Timothy D. Johnson,1 Bhavini Patel2

1. Telethon Kids Institute, University of Western Australia
2. Northern Territory Department of Health

Benzathine benzylpenicillin G (BPG) is a beta-lactamase antibiotic developed in 1951.1 Administered intramuscularly, BPG has low in vivo solubility, producing prolonged serum penicillin concentrations. This makes BPG suitable for treating penicillin-sensitive organisms responsive to extended, low serum penicillin concentration. In Australia, BPG licence indications include mild-moderate group A streptococcal (GAS) infections (pharyngitis) and treponemal infections (syphilis, yaws, bejel and pinta).2 BPG is also indicated for people with a history of acute rheumatic fever (RF) and rheumatic heart disease (RHD) as secondary prophylaxis against GAS infections that can precipitate a recurrence of RF. The World Health Organization (WHO) considers BPG an essential medicine.3

Worldwide, two formulations of BPG are available.4 In low resource settings, relatively affordable, generic, lyophilized powders are widely used. The powdered formulations are reconstituted into an aqueous suspension immediately prior to administration and do not require a cold chain. A branded liquid formulation is available in some high resource settings. Produced by a single manufacturer, the liquid formulation of BPG is relatively expensive and requires refrigeration.

In Australia, a single or short course of BPG injections is recommended for management of syphilis, skin sores and pharyngitis.2 An extended course of BPG is indicated for secondary prophylaxis against recurrent RF.5 In susceptible young people, RF can be precipitated by an abnormal immune reaction to GAS infection, causing fevers, arthralgia, carditis, neurologic (chorea) and cutaneous symptoms. Cardiac involvement of RF causes progression to heart valve damage in RHD. Recurrences of RF accelerate calcific disease; without treatment RHD culminates in heart failure and increases the risk of arrhythmias, infective endocarditis and stroke. Women with RHD are at increased risk of heart failure and death during pregnancy and delivery. In Australia, Aboriginal and Torres Strait Island communities live with some of the world’s highest burden of RHD.6

High-quality secondary prophylaxis with BPG can prevent recurrences of RF and slow the progression of RHD.1 Australian guidelines recommend that any person with a history of RF or RHD receive 1.2 IU of BPG every 28 days for 10 years after the most recent episode of RF or until the age of 21 years, whichever is longer. Delivery of scheduled secondary prophylaxis against RF has been the focus of Australia’s National RF Strategy since 2008. Commonwealth investment in the national coordinating unit (RHD Australia) and four jurisdictional programs will total $24 million between 2008 and 2016, as indicated in an email from Claire Boardman, Deputy Director of RHD Australia (claire.boardman@menzies.edu.au) in August 2014. A number of research programs to improve quality of clinical care and adherence with scheduled BPG injections have occurred over the past decade.7 Reliable supplies of BPG are essential for delivering the recommended schedule of secondary prophylaxis for people living with RHD. In the Australian context, an unreliable supply of BPG represents an important public health issue – particularly in the context of Indigenous health – and in doing so highlights an important unintended health disparity.

This mixed methods review describes national access to BPG in Australia from 1994 to 2014 and explores implications for providing RHD secondary prophylaxis programs.

Methodology
A PubMed search for ‘benzathine AND penicillin AND Australia’ did not identify any relevant articles. Grey and informal literature was identified on Google search using the search terms ‘benzathine penicillin G’, ‘Bicillin LA’, ‘Pan Benz’; ‘Pan Benzathine penicillin’, ‘stock outs’, ‘shortage(s)’, ‘disruption(s)’, ‘AND’ ‘Australia’. Bibliographic review identified key references, including one article quantifying the number of doses of BPG administered through the Northern Territory RHD Control Program.8 Correspondence and memoranda from drug manufacturers was also identified. Individuals and institutions were approached for specific source material where possible. Additional documents were sought from the Therapeutic Goods Administration (TGA) under a freedom of information request.9 Literature review was correlated with quantitative data extracted from the Pharmaceutical Benefits Scheme (PBS) database ‘PBS Statistics – Item Reports’.10 Archival review of PBS schedules (January 2004 – August 2014) identified all relevant schedule item numbers for Bicillin L-A and Pan Benzathine Penicillin (Pan Benz). These product codes were used to generate PBS Item Reports by selecting for item number, report on services, report format by scheme and month (rows) by state (columns), Start date: January 1994, End date: August 2014.

Results

Qualitative
Prior to 1994, Australian clinicians decanted half a 4 mL formulation of Bicillin L-A (developed for the treatment of syphilis) into a 2 mL preparation to administer secondary prophylaxis against RF.12 Health professionals from the Aboriginal Medical Services and Government Health Services advocated for a more appropriate 2 mL preparation to be introduced for RHD control.12,13 Support from the then licence holder Wyeth and the TGA in 1994 ensured a 2 mL formulation of Bicillin L-A BPG became available in Australia in 1995.14 There is no record of supply interruptions to the new Bicillin L-A product in the 1990s. Supply of Bicillin L-A appears to have been erratic in the early 2000s. Specific shortages have been described in 2001 and again in 2004, both requiring restricted use of the drug.12,15 Clinicians reported concern about contingency measures for accessing BPG in the absence of Bicillin L-A supply.12

In 2005, global production of Bicillin L-A was transferred from Wyeth to King Pharmaceuticals.16 The sales and distribution for Bicillin L-A in Australia were transferred to Aspen Pharmacare, which managed the King Pharmaceutical portfolio.16 Changes in distribution responsibilities were communicated to Australian practitioners at short notice.13 The existing stockpile of Bicillin L-A was transferred to Aspen Pharmacare and was expected to be sufficient until the end of May 2006.13 In 2006, Wyeth ceased production of Bicillin L-A in the United States. King Pharmaceuticals established a new manufacturing location for Bicillin L-A in the United States. This change in location appears to have been associated with reduced supply of the product.17
Revisions to manufacturing location also necessitated an updated regulatory submission to the TGA. This process was delayed and Bicillin L-A was unavailable in Australia from about May 2006 until it was reintroduced on 1 April 2008.16

In the interim, a powdered formulation – Pan Benzathine Benzylpenicillin (Pan Benz) – was secured from a French company with TGA and GMP certification.16 The TGA granted an exemption under the Therapeutic Goods Act 1989 Section 19A (‘Exemptions where unavailability, etc, of therapeutic goods’) to make the product available in Australia.16 This Pan Benz product required suspension in 4.6 mL of water, more than twice the volume of the previous Bicillin L-A formulation. A number of anecdotal concerns were raised about the use of Pan Benz, particularly of the previous Bicillin L-A formulation. A change in manufacturing practices and administering BPG. Concerns about acceptability and administration of the drug were widespread. Since the reintroduction of Bicillin L-A in 2008, briefer periods of shortage have occurred and the impact has been mitigated by careful management of the product at a pharmacy level, as communicated in an email by Bhavini Patel, NT Department of Health (bhavini.patel@nt.gov.au) in September 2014. The most recent two shortages have been formally notified by Pfizer and attributed to shortages associated with interruptions of supply.21 The first shortage was communicated to health professionals by Dr Nick Fletcher, Associate Medical Director, Pfizer Established Products, (facsimile December 2012). Further expected shortages of BPG were again experienced in 2014 in the period of 11 March to 5 April.21

**Quantitative data**

Archival PBS schedule review identified eight relevant product codes for BPG: Bicillin L-A (8167W), Pan Benz (9002T), Bicillin L-A (5025L), Pan Benz 900 mg (5252K), Bicillin L-A (8743E), Pan Benz 900 mg (9003W), Bicillin L-A (2267H), Bicillin L-A (5027N). Manual review identified deletions, additions and alterations to manufacturers’ codes in the PBS Schedule of Pharmaceutical Benefits. Monthly PBS usage data for the three major codes (8167W, 9002T and 2267H) were extracted from the online BPS database and are presented in Figure 1.

A targeted extraction of PBS data on BPG use in the Northern Territory was correlated with published BPG administration data from the Northern Territory RHD control program 2007–2010. PBS records of BPG supplied in the Northern Territory show a significantly lower number than the total number of doses recorded as administered by the Northern Territory control program over the same period.22

**Discussion**

The TGA defines medication shortage in Australia as occurring when ‘the supply of medicine is not reasonably likely to meet the normal or projected consumer demand for the medicine within Australia for a period of time’.23 This review has identified five periods of shortage of BPG in Australia since 1995. Two shortages in 2001 and 2004 appear to have been relatively short and associated with only minor disruption to services. The cause of these shortages is unclear. The two year stock-out between 2006 and 2008 was reportedly caused by a change in manufacturing practices and regulatory delays in TGA submission. These delays necessitated the introduction of a new powdered formulation to ensure supply of BPG. The change to a powdered formulation necessitated rapid communication with health staff responsible for prescribing and administering BPG. Concerns about acceptability and administration of the drug were widespread. Since the reintroduction of Bicillin L-A in 2008, briefer periods of shortage have occurred and the impact has been mitigated by careful management of the product at a pharmacy level, as communicated in an email by Bhavini Patel, NT Department of Health (bhavini.patel@nt.gov.au) in September 2014. The most recent two shortages have been formally notified by Pfizer and attributed to shortages associated with interruptions of supply.21 The first shortage was communicated to health professionals by Dr Nick Fletcher, Associate Medical Director, Pfizer Established Products, (facsimile December 2012). The second communication to healthcare professionals was released in April 2014.

There is no single unified data source to quantify medication use and supply in Australia. PBS data can be extracted to account for items issued through the PBS and RPBS. However, PBS data does not include medications dispensed through the Remote Area Aboriginal Health Services (RAAHS) functioning under Section 100 of the National...
robustly demonstrated. The importance of BPG delivery is recognised as a health quality measure: delivery of >80% of scheduled injections is a key performance indicator for primary health services and jurisdictional RHD control programs in Australia. Achieving this goal requires tremendous investment of human, economic and social resources. Shortages, stock-outs and supply instability of BPG undermine this investment, generate confusion and may cause adverse health outcomes for individuals.

This review is limited by heavy reliance on anecdotal and informal data to understand the cause, context and duration of stock-outs. These limitations reflect the perpetual challenge for Australian clinicians and public health agencies to describe, monitor and optimise BPG supply over two decades. The Medicines Shortages Information website has the potential to provide a valuable archive of drug shortages in the future, although the utility for frontline clinicians is yet to be understood. Inclusion of medicines dispensed via RAHS under Section 100 in PBS figures would provide a more complete picture of medication use throughout Australia.

Conclusions

BPG has been the mainstay of management for RF and RHD in Australia for two decades. Delivering this disease altering intervention for vulnerable populations is a critical challenge for the health system. It is unconscionable that the challenge has been repeatedly amplified by inadequate access to appropriate medication. A reliable, predictable supply of BPG is a prerequisite to addressing this disease which so powerfully illustrates Australia’s Indigenous health disparity. Actions may include incorporating RAHS data in PBS records, scoping back-up suppliers for BPG and supporting implementation of the Medicines Shortages Information website.

References

5. Rheumatic Heart Disease Australia. Australian Guidelines for Prevention, Diagnosis and Management of Acute Rheumatic Fever and Rheumatic Heart Disease. 2nd ed. Casuarina (AUST): Menzies School of Health Research; 2012.