Record of the Anti-Infective Subcommittee of PTAC meeting held at PHARMAC on 10 May 2019

(minutes for web publishing)

Anti-Infective Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.*

Note that this document is not necessarily a complete record of the Anti-Infective Subcommittee meeting; the relevant portions of the minutes relating to Anti-Infective Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Anti-Infective Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes was reviewed by PTAC at its meeting on 21 and 23 August 2019, the record of which is pending and will available on the PHARMAC website when finalised..

Present from the Anti-Infective Subcommittee:
Sean Hanna (Chair, PTAC Member)
Emma Best
James Chisnall
Edward Gane
Tim Matthews
Graham Mills
Jane Morgan
Nigel Patton
Howard Wilson

Apologies:
Simon Briggs (via teleconference)
Anja Werno

Summary of recommendations

3.5 The Subcommittee **recommended** that fosfomycin trometamol ('fosfomycin') be funded for the treatment of uncomplicated urinary tract infections (UTIs) with a high priority. The Subcommittee made this recommendation based on the need for another sequential agent for the treatment of uncomplicated UTIs caused by multi-drug resistant microorganisms in adults, particularly in women with recurrent UTIs, and in children. The Subcommittee made this recommendation subject to the following criteria:

> **Restricted**
> Initiation On the recommendation of clinical microbiologist or infectious disease specialist,
> All of the following:
> 1. Patient has an acute, symptomatic, bacteriologically-proven uncomplicated urinary tract infection (UTI); and
> 2. The bacteria, based on the microbiology report, is resistant to all other antibiotics including nitrofurantoin; or
> 3. The patient has a contraindication or documented intolerance to all UTI antibiotics including nitrofurantoin.
>
> Note: Fosfomycin should not be used for first-line treatment. Upon request, microbiology should report fosfomycin sensitivity for patients with resistant infections.

4.4 The Subcommittee **recommended** that fosfomycin (Fomicyt or Fosmicin) for salvage therapy for infections caused by CRE be deferred due to insufficient evidence for the use of fosfomycin for this indication at this time. The Subcommittee considered that it would welcome a new funding application including further clinical trial data supporting the use of fosfomycin for this indication, once published.

4.5 The Subcommittee **recommended** that ceftazidime with avibactam (Zavicefta) for salvage therapy for infections caused by CRE be funded with a high priority due to the need for a last-line treatment option for this indication and evidence of efficacy. The Subcommittee made this recommendation subject to the following restrictions:

> **Restricted**
> **Initiation**
> Clinical microbiologist or infectious disease specialist.
> All of the following:

1. Proven resistant micro-organism, based on microbiology report; and
2. Proven infection with carbapenem-resistant *Enterobacteriaceae* (CRE); and
3. Ceftazidime with avibactam will not be used for prophylaxis; and
4. Treatment with colistin is clinically inappropriate.

Note: Where appropriate, treatment with ceftazidime with avibactam should be administered in combination with aztreonam, if available.

4.6 The Subcommittee **recommended** that ceftolozane with tazobactam (Zerbaxa) for significant infections due to multidrug-resistant aerobic Gram-negative organisms, including *Pseudomonas aeruginosa* and extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, be declined.

5.4 The Subcommittee **recommended** that the antiretroviral Special Authority criteria for nPEP be amended, to closer align with the UK and ASHM guideline risk assessment tool, with a high priority to include:

a) for source partners with a known positive HIV status (viral load greater than 200 copies/ml): receptive and insertive anal sex or receptive vaginal sex;

b) for source partners with an unknown HIV status to include; receptive anal sex with a person from a high HIV prevalence country or high HIV prevalence risk group.

5.5 The Subcommittee **recommended** that initiating Special Authority for PrEP and nPEP be widened to include sexual health specialist, infectious disease specialists and vocationally registered general practitioner or nurse practitioner.

5.6 The Subcommittee **recommended** that the Special Authority criteria for antiretrovals be separated into two groups:

a) Confirmed HIV, prevention of maternal transmission and percutaneous exposure which should still be limited to named specialists;

b) PrEP and PEP where sexual health specialists, infectious disease specialists, vocationally registered general practitioners or nurse practitioners can initiate patients.

6.4 The Subcommittee recommended that the application for oseltamivir for the treatment and prophylaxis of patients in long term care facilities (LTCFs) during influenza outbreaks within the facility be declined due to insufficient evidence of benefit in this patient group and treatment setting.

1. Therapeutic Group and NPPA Review

1.1. The Subcommittee noted the main contributors to the gross pharmaceutical expenditure in the Infections – Agents for Systemic Use therapeutic group.

Antibacterials

1.2 Members noted the high expenditure on cephalosporins and noted that the use by indication is not captured. The Subcommittee noted that it would like to be able to provide recommendations and advice to PHARMAC on the rationale for growth in use and possible restrictions that would provide aid in appropriate use of these antibiotics. Members considered that there is likely to be inappropriate use, however without indication data it is impossible to pinpoint exact clinical areas where it is occurring.

1.3 The Subcommittee recommended that PHARMAC engage with a primary care quality programme such as 'Health Care Homes'. Members considered that a programme to link indications to prescribing data capture and surveillance, and further continuing education such as BPAC articles are needed to reiterate the need for careful consideration of the antibiotic choices made in primary care.

1.4 The Subcommittee noted that PHARMAC has received a tender bid for Amoxicillin clavulanate (amoxicillin 400 mg with clavulanic acid 57 mg per 5 ml) grans for oral liquid twice daily formulation. The Subcommittee noted that there is currently a 125 mg per 5 ml and a 250 mg per 5 ml three times per day presentation listing on the pharmaceutical schedule. Members supported a twice daily formulation as it would be more suitable for administration to paediatric patients (such as around school/ daycare hours without a midday dose) and that twice daily was more simple for adherence for families. The increased amoxicillin component (7:1) compared to the usual 4:1 ratio could also offer an advantage for some clinical situations requiring higher amoxicillin dosing where the oral dose is limited by the clavulanate component (such as complicated ORL conditions with penicillin-reduced-susceptibility pneumococci). Members considered that, if this formulation was funded, it would not mean that other formulation could be delisted as these are required for other patient groups in particular the 125mg per 5 ml TDS syrup formulation to enable dosing of smaller infants. A large amount of education about prescribing would be required if the twice daily formulation syrup was introduced. There is potential for community use at both ends of the age spectrum and an understanding by clinicians requiring the switching of patients that could not tolerate tablets, which are three times per day, to twice daily syrup.

Anti-fungals

1.5 The Subcommittee noted the IV antifungal usage in the 2018 financial year. Members noted that overall there had been some significant decreases in gross expenditure as a result of PHARMAC Tendering these products. Members discussed Liposomal Amphotericin B and noted that there had been a reduction in expenditure. Members considered that this is likely due to posaconazole prophylaxis being available for use in high risk patients, resulting in a reduced incidence of invasive fungal disease.

Antimalarials/antiparasitics

1.6 The Subcommittee noted the expenditure on the antimalarial and antiparasitic groups, Members had no further comments.

Antiretrovirals

1.7 Members noted that PHARMAC had recently run an RFT for the antiretrovirals market which excluded the integrase strand transfer inhibitors (dolutegravir and raltegravir). Members noted the high expenditure for integrase strand transfer inhibitors and considered it would be possible to run a competitive process for these two chemicals which could result in a 'first line, second line' situation for existing and new patients.

1.8 The Subcommittee considered that, if a competitive process was run for dolutegravir and raltegravir chemicals, it would be important that they are both still available for some small patient groups such as women wanting to become pregnant and people with viral resistance. Members considered that patients could switch between chemicals with it being reasonably straight forward to switch a patient from dolutegravir to raltegravir. However, Members considered that switching patients

between chemicals would require a consideration of the potential problems which may occur, including the possibility of pregnancy, resistance issues and pill burden. Members considered that some further advice from this Subcommittee would be required in the development of a competitive process but considered that it was supportive if this competition brought savings and maintained appropriate access of the Integrase Stand Transfer Inhibitor chemical to the patients that needed it.

1.9 The Subcommittee noted that pill burden is an important consideration in a competitive process in the HIV treatment area. Members noted that adherence to treatment can be affected by number and frequency of tablets patients are required to take particularly for lifelong medication, Members considered that it is desirable for there to be a small number of tablets (one to two) to be taken once per day.

1.10 Members considered that if a competitive process was progressed, then PHARMAC should engage with the New Zealand Aids Foundation as they are an important stakeholder representing patients living with HIV.

Antivirals

1.11 The Subcommittee noted that aciclovir expenditure should be further reducing as a result of the listing of valaciclovir in the 2016. Members noted that valaciclovir is a prodrug of aciclovir and has improved bioavailability; members recommended that educational materials such as a BPAC article should be provided to prescribers on this topic. In addition contact had been made with the NZ formulary to provide advice for dosing of children aged 2-12 years with valaciclovir (not currently available on NZFc)

Treatments for hepatitis B

1.12 The Subcommittee noted that PHARMAC completed an RFP for entecavir and tenofovir in 2018 which resulted in significant savings for the hepatitis B treatments market. Members noted that approximately 3500 patients are on PHARMAC funded treatment for chronic hepatitis B (HBV), although the estimated prevalence is over 100,000, many of whom are undiagnosed. Members considered that even with a vaccine available it would still be a long time (approximately 90 years) before the disease is eradicated in New Zealand and noted that there is a large prevalent pool of patients already infected.

1.13 The Subcommittee considered that, since the RFP for entecavir and tenofovir disoproxil, which has meant that there is no Restrictions on these chemicals and that primary care need to be further educated on the use of these chemicals. The Subcommittee considered that lamivudine tablet Special Authority is no longer required as patients would be using either entecavir or tenofovir disoproxil as treatment for hepatitis B and prophylaxis of reactivation.

1.14 Members noted that the number of adults enrolled in the National HBV Surveillance Programme continues to increase as is the incidence of HBV related liver complications such as hepatocellular carcinoma. Members noted that immigration has an impact on the disease prevalence of HBV in New Zealand and noted that an improvement in Asia Pacific vaccination programmes would help.

1.15 Members noted that current treatments for HBV are entecavir and tenofovir which are lifelong therapies to suppress the cccDNA reservoir. Members noted that future

therapies are being studied to reach an end-goal of Sterilising Cure, which would include the clearance of integrated HBV DNA. Members noted that these therapies are still some years away however PHARMAC should consider its commercial options to treat this disease noting that the prevalence is approximately twice that of hepatitis C and therefore the budget impact of these cures would be significant. Members also noted that the likely cost effectiveness of cure would be similar to that of hepatitis C, as curing the disease has flow on impacts such as a reduction in health system costs, including monitoring and liver transplantation.

Treatments for chronic hepatitis C

1.16 The Subcommittee noted the large uptake of chronic hepatitis C patients being treated since the listing of a pangenotypic treatment on 1 February 2019. The Subcommittee noted that, to date, primary care has accounted for over a third of patients being commenced on treatment and that treatments has resulted in a 96% cure rate.

1.17 Members also noted that a hepatitis C action plan is currently in development and being led by the Ministry of Health which aims to be presented to the Minister of Health in late 2019. Members noted that the aim of this action plan is to increase awareness of the disease and to treat more patients which would put New Zealand on track to meet the WHO goals for hepatitis C elimination.

1.18 The Subcommittee considered that the unmet need in hepatitis C is for patients that have not achieved SVR and cannot be re-treated with existing direct acting antivirals. The Subcommittee considered that the patient cohort who do not achieve SVR may have been treated by Viekira Pak +/- ribavirin, Harvoni, imported DAA themselves or Maviret. Members considered total number of patients not achieving SVR to date is150 and that the majority of these patients (95) have been treated with Viekira Pak (+/- ribavirin). Member noted that the ongoing rate of patients not achieving SVR is likely to reduce significantly as the cure rate for Maviret is much higher (99.7%) than with Viekira Pak (97%).

1.19 The Subcommittee considered that patients who complete a course of Viekira Pak +/- ribavirin, do not achieve SVR and have NS5A/NS3 resistance have two current treatment options available to them: sofosbuvir/velpatasvir/voxilaprevir (Vosevi) for 12 weeks or sofosbuvir plus glecaprevir/pibrentasvir (Maviret) and ribavirin for 12 weeks. Members noted that Vosevi has been considered by PTAC already and the use of sofosbuvir with Maviret and ribavirin has been considered in the MAGELLAN studies (de Ledinghen et al. J hepatol. 2018; 68(supp 1):S23) which consider the inclusion of sofosbuvir and the duration of 12 or 16 weeks with treatment outcomes. Members noted that the inclusion of sofosbuvir to the Maviret and ribavirin regimen increases the SVR rate from 80% to 100%. Members also noted that there was no difference between 12 and 16 weeks treatment in these patient groups.

1.20 Members considered that if no NS5A resistance associated variants (RAVs) are detected then patients can be retreated with Maviret for 16 weeks. The Subcommittee noted that these combinations (Vosevi or sofosbuvir with Maviret and ribavirin) would not be suitable for patients who have decompensated liver disease. Members noted that the number of decompensated patients has decreased. Members noted that 50% of genotype 3 patients have relapsed after being treated with ledipasvir with sofosbuvir and ribavirin as opposed to 92% achieving SVR in genotypes 1,2,4 and 6. Members noted that sofosbuvir with velpatasvir (Epclusa)

with ribavirin has improved outcomes in these patients groups with 85% achieving SVR.

1.21 The Subcommittee noted that PHARMACs ongoing need for ribavirin would need to be considered with respect to future treatment options. PHARMAC should expect that there would be up to 2-3 patients per month in New Zealand that arrive in secondary care in a decompensated state that would need ribavirin co-prescribed with Harvoni treatment. Members noted that if Harvoni was replaced with Epclusa, ribavirin would still be required for these patients. For patients that require retreatment after unsuccessful first line DAA treatment, the ongoing need for ribavirin would depend on whether Vosevi (no ribavirin) or sofosbuvir with Maviret (with ribavirin) is used.

Urinary Tract infections

1.22 The Subcommittee consider that the use of trimethoprim had plateaued since 2015 however the non-subsidised (via pharmacies) usage was not available, Members considered that this Subcommittee review the usage of trimethoprim over the counter and that PHARMAC should endeavour to get usage data from retail pharmacy groups and that this should be made an action point. Members also noted that resistance rates have continued to rise and questioned whether it is still appropriate for trimethoprim to still be available over the counter at pharmacies. Members also considered that DHBs develop their recommendations for first line treatments based on resistance rates and did not consider that this was happening in pharmacies. Members recommended that PHARMAC provide to the Medicines Classification Committee the Anti-infective Subcommittee's concerns regarding the availability of trimethoprim over the counter and recommended it should only be available on a prescription.

1.23 The Subcommittee noted that nitrofurantoin 50 mg use had risen and has a higher efficacy than trimethoprim albeit requiring longer duration of treatment and being a four times per day formulation. The Subcommittee noted that if PHARMAC were to list the twice daily nitrofurantoin formulation it would see many more prescribers use it first line. It has also a first line agent recommendation for UTI treatment in the BPAC antibiotic guidelines, some hospitals and several regional pathway guidelines due to trimethoprim resistance. The Subcommittee considered that education should be provided to prescribers if a listing is progressed.

Cephalexin

1.24 The Subcommittee noted that this Subcommittee had recommended that cephalexin oral liquid should be available on a PSO and that PTACs view was that it should not be made available via PSO as patients who are sick enough to require emergency treatment should be seen in hospital noting that in areas designated as rural, surgeries can have anything that they consider appropriate on PSO. The Subcommittee disagreed with this approach as they considered that access to cephalexin oral liquid on PSO would allow some patients treatment they could avoid the need to go to hospital at all.

1.25 The Subcommittee noted that that flucloxacillin liquid is available on PSO but it is unpalatable very difficult to get adherence to treatment in paediatric patients. Members noted that management of skin and soft tissue infections is likely amongst the most common and important conditions affecting those with socioeconomic disadvantage who may access healthcare outside of working hours; in particular

children of Maori and Pacific ethnicity who experience the highest burden of skin and soft tissue issues and complications. Members noted that skin infections and their complications are one of the commonest reason for hospitalisations in children and are known to lead to sequelae such as Poststreptococcal glomerulonephritis (PSGN) and tenuously also to Acute rheumatic fever (ARF).

Valganciclovir – congenital CMV

1.26 The Subcommittee noted an increase in the number of applications received for valganciclovir for infants with congenital cytomegalovirus. To date PHARMAC have received and approved four applications for infants with congenital CMV. Approval has been given noting the lack of suitable long term treatment options in the community, given ganciclovir is the only funded treatment and is given via intravenously. The Subcommittee recommended widening of access for this patient group with a high priority. Member considered that a Special Authority would need to be developed and criteria used internationally have clear recommendations, Members considered that Paediatric Infectious Disease involved would be required.

1.27 Members noted that valganciclovir needs to be compounded into an oral liquid formulation for use in paediatric patients for congenital cytomegalovirus, under NPPA approval; and post transplant or immunocompromised patients; under the current Schedule criteria. Members noted that the compounding of valganciclovir oral liquid requires cytotoxic safety precautions which is not available at all DHB hospitals and ADHB hospital pharmacy current provide this service for North island patients who would otherwise need to pay for the large compounding fees charged by outsourced compounding providers. Members noted that this service provided by ADHB causes significant resourcing burden which it should not have to carry. Members considered that PHARMAC should try to obtain an oral liquid which would be useful for the compounding issues highlighted.

2 Correspondence and Matters Arising

Gemini study – Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection

2.2 The Subcommittee considered Gemini I and II, a non-inferiority study of dolutegravir with lamivudine vs dolutegravir with tenofovir and emtricitabine in 719 and 722 HIV-1 treatment naïve adults at 48 weeks. (Cahn et al. Lancet. 2019;393:143-55). Members consider the study was small and the follow up period was short and most clinicians would like to see a longer follow up period before being comfortable using dual therapy.

2.3 The Subcommittee considered that there were likely to be different levels of acceptance of dual therapy across the DHBs, noting that Members are aware of some using dual therapy already. The Subcommittee considered that this regimen could be used within the current funding restrictions and that it would be up to the individual clinician's comfort with the available evidence for the regimen.

Valganciclovir use during steroid pulse therapy to prevention lung graft rejection

2.4 The Anti-infective Subcommittee noted that this Subcommittee had declined an application in November 2015 which consideration the widening access of valganciclovir to lung transplant recipients who require valganciclovir prophylaxis to

prevent cytomegalovirus (CMV) reactivation when receiving steroid pulse therapy for late acute rejection. Members noted that this application had come from a respiratory physician and was reviewed by the Transplant Immunosuppressant Subcommittee in May 2015 which recommended widening of access and did not provide a priority.

2.5 Members also noted that, in October 2017, the Transplant and Immunosuppression Subcommittee considered evidence in this treatment setting and recommended funding with a high priority which PTAC accepted this recommendation in August 2018. Members noted the following recommendations:

- The Subcommittee recommended that funding of oral valganciclovir be widened to include CMV prophylaxis for all transplant patients receiving pulse methylprednisolone for acute rejection after the initial course of CMV prophylaxis (variable depending on the organ) that requires a further 90 days of valganciclovir for CMV prophylaxis with a high priority.

- The Subcommittee recommended that funding of oral valganciclovir be widened to include an additional 6 months of initial CMV prophylaxis for lung transplant patients (12 months total from time of transplant) if the quantiferon CMV-approach is used to determine prophylaxis requirement with high priority.

2.6 The Subcommittee questioned the availability of the quantiferon-CMV in New Zealand and noted that labs would struggle to get the samples sent to Australia and have results back in a time for they to be useful. Members consider that this should be resolved before any changed to criteria are made.

2.7 The Subcommittee considered there is poor evidence in this treatment setting and noted that in a transplant situation there are complex considerations which are more appropriated managed by the transplant team. Members noted that PTAC had accepted the recommendation from the Transplant and Immunosuppression Subcommittee based on expert opinion.

Topical Antibiotics

2.8 The Subcommittee noted that PHARMAC has tendered mupirocin ointment for a 5 g pack size, noting that the current listed formulation is a 15 g pack. The Subcommittee considered that a 5 g pack size would be sufficient for any indication required although they considered that it should only be used for MRSA decolonisation. The Subcommittee recommended that there should be more education provided to primary care of the use of topical antibiotics. Members considered that at present the part charge provides a barrier to discourage inappropriate use and they recommended that restricting it further for use only under the recommendation of an ID physician or microbiologist would help.

Moxifloxacin for splenectomy patients with confirmed allergy to penicillin

2.9 The Subcommittee noted that patients with a confirmed allergy to penicillin who have had a splenectomy would require a stat dose of 400 mg moxifloxacin. Members noted that if they were awaiting the results of other investigations they may require 400 mg moxifloxacin for multiple days. Members did not consider it would be an ongoing course as reported in some guidelines.

Vancomycin for infected arthroplasty

2.10 The Subcommittee noted a funding application from a clinician to consider the funding of a larger size of vancomycin vials (5 g and 1 g) for use in bone cement in prosthetic joint infections. Members noted that the current listing is for a 500 g size and that the application considered that a larger size would reduce the staff time for opening multiple vials (up to 30 vials for large spacers) and would also reduce the contamination risk associated with opening multiple vials. The Subcommittee considered that this was a reasonable request however it also considered that if the larger vials were listed it would need to be cost neutral to the current listings. The Subcommittee recommended that PHARMAC include the larger pack sizes in the next Invitation to Tender to consider if a cost neutral price could be achieved.

Correspondence

Clarithromycin oral liquid – Helicobacter pylori

2.11 The Subcommittee noted correspondence from a clinician regarding the lack of availability of clarithromycin oral liquid for use in Helicobacter pylori eradication, noting that it is the medicine of choice for this indication. The Subcommittee considered that while the oral liquid is listed for other indications, it should also be made available for *Helicobacter pylori* eradication. The Subcommittee considered that this was a reasonable request and confirmed that clarithromycin is a first line agent for H*elicobacter pylori* eradication, noting that it is uncommon for children to be treated for this condition, therefore the budget risk was small. The Subcommittee recommended that clarithromycin oral liquid Special Authority should be widened to include *Helicobacter pylori* eradication in patients who cannot swallow tablets or capsules.

Clarithromycin oral liquid – Prophylaxis of bacterial endocarditis in dental procedures

2.12 The Subcommittee noted correspondence from a clinician requesting that clarithromycin oral liquid should be made available for prophylaxis of bacterial endocarditis in outpatient dental procedures when amoxicillin is contraindicated, in cases such as allergy. The Subcommittee considered that this situation is uncommon and it is sensible for clarithromycin oral liquid to be available for these patients. The Subcommittee recommended that a change is made to the Special Authority for clarithromycin oral liquid to enable access for patients with confirmed allergy to penicillin and requiring prophylaxis of bacterial endocarditis.

TB and multi-drug resistant regimens – correspondence from the NZ clinical TB network

2.13 The Subcommittee noted feedback from the NZ clinical TB network voicing some concern over declined NPPA applications for bedaquiline and linezolid where the World Health Organisation had recommended these treatments should now be used in Multi-drug resistance TB (MDR-TB). Members noted that these applications had been further considered by PHARMAC once additional information had been provided on the funded alternatives.

2.14 The Subcommittee noted that the NZ clinical TB network were considered submitting a funding application for both of these pharmaceuticals for MDR-TB and that it supported an application being provided. Members considered that TB has a large public health risk associated which can also impact patients ability to travel. Members noted that PHARMAC has considered and approved bedaquline for extensive multi-drug resistance TB (XMDR-TB) and that MDR-TB is still a small group of patients in NZ (approximately 4 per year). The Subcommittee noted that all patients would get 24 weeks of bedaquiline and one third would have 4-6 week

of linezolid, one third would have three months of linezolid and one third would have 18 months of linezolid. The Subcommittee also noted that amikacin had a lot of issues associated with its IV use and toxicity.

3 Fosfomycin trometamol for the first-line treatment of uncomplicated urinary tract infections

Application

3.2 The Subcommittee reviewed the application from Te Arai BioFarma for fosfomycin trometamol ('fosfomycin') for the first-line treatment of uncomplicated urinary tract infections (UTIs).

3.3 The Subcommittee noted that PHARMAC received several items of correspondence from the applicant regarding the proposed place of fosfomycin in therapy:

3.3.1 First correspondence: fosfomycin as a first- or second-line option for uncomplicated UTIs.

3.3.2 Second correspondence: fosfomycin as a second-line option after nitrofurantoin failure or where there is a contraindication or intolerance to other treatment options.

3.4 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

3.5 The Subcommittee **recommended** that fosfomycin trometamol ('fosfomycin') be funded for the treatment of uncomplicated urinary tract infections (UTIs) with a high priority. The Subcommittee made this recommendation based on the need for another sequential agent for the treatment of uncomplicated UTIs caused by multi-drug resistant microorganisms in adults, particularly in women with recurrent UTIs, and in children. The Subcommittee made this recommendation subject to the following criteria:

Restricted
Initiation On the recommendation of clinical microbiologist or infectious disease specialist.
All of the following:

4. Patient has an acute, symptomatic, bacteriologically-proven uncomplicated urinary tract infection (UTI); and
5. The bacteria, based on the microbiology report, is resistant to all other antibiotics including nitrofurantoin; or
6. The patient has a contraindication or documented intolerance to all UTI antibiotics including nitrofurantoin.

Note: Fosfomycin should not be used for first-line treatment. Upon request, microbiology should report fosfomycin sensitivity for patients with resistant infections.

3.6 The Subcommittee noted that fosfomycin was listed on the Hospital Medicines List (HML) from 2013, and that PHARMAC received correspondence in 2016 from the Canterbury DHB Antimicrobial Stewardship Committee regarding access to fosfomycin in the community. The Subcommittee noted that a proposal for fosfomycin to be listed in Section B of the Pharmaceutical Schedule is currently ranked on PHARMACs Options for Investment list (with use restricted to treatment

of patients with acute symptomatic bacteriologically-proven lower UTIs and with proven resistance or contraindication to all other oral antibiotics including nitrofurantoin, on the recommendation of an Infectious Disease physician or Clinical Microbiologist).

Discussion

3.7 The Subcommittee noted that a urinary tract infection (UTI) is either an infection of the bladder and lower urinary tract (cystitis) or an infection of the kidney and upper urinary tract (pyelonephritis), and that most UTIs are due to colonisation by pathogenic *Escherichia coli (E. coli)*.

3.8 The Subcommittee noted that UTIs are classified as uncomplicated if there is no functional or anatomical abnormality in the urinary tract, no evidence of pyelonephritis, no renal functional impairment, and no concomitant condition that would promote a UTI. The Subcommittee noted that, if an uncomplicated UTI is left untreated, complications such as pyelonephritis, kidney damage, bacteraemia, and sepsis can develop.

3.9 The Subcommittee noted that the incidence of uncomplicated UTIs is very high, although most cases are mild and some require symptom management alone. The Subcommittee considered that approximately 200,000 patients each year are treated with funded antimicrobial agents for uncomplicated UTI according to community pharmacy claim data. The Subcommittee considered it was difficult to determine what proportion of antimicrobial agent use is for treatment of uncomplicated UTI (compared to prophylaxis).

3.10 The Subcommittee noted that the incidence of uncomplicated UTI is much higher in women and would account for more than 80% of cases. The Subcommittee noted that a UTI occurring in pregnancy is a complicated UTI and that treatment of complicated UTIs is outside the requested indication for this application.

3.11 The Subcommittee considered that uncomplicated UTIs do not disproportionately affect Māori or Pacific people. The Subcommittee considered that patients with lower socio-economic status may have an increased risk of complications if they have difficulties in accessing healthcare.

3.12 The Subcommittee considered that New Zealand adult patient with uncomplicated UTIs due to *E. coli* would receive treatment with either trimethoprim (between 65% and 70% of cases), nitrofurantoin (30% of cases) or cefalexin (less than 5% of cases). The Subcommittee considered that other agents such as quinolones or amoxicillin with clavulanic acid may be used for first-line treatment of uncomplicated UTIs in a small number of cases and co-trimoxazole, amoxicillin with clavulanic acid, or cefaclor were commonly used in young children (syrup formulations) with nitrofurantoin increasingly being required due to resistance. The Subcommittee considered that standard of care second-line therapy for uncomplicated UTIs in New Zealand adults would be with nitrofurantoin (if not used first-line) rather than with norfloxacin.

3.13 The Subcommittee noted that the 2017 Canterbury Antimicrobial Susceptibility Report demonstrated that antimicrobial resistance (predominantly of *E. coli)* is climbing but has been relatively stable since 2009, reporting resistance rates in Canterbury of around 25% to trimethoprim and 4% to nitrofurantoin. Members considered that resistance to fosfomycin, which is currently used in New Zealand

under Section 29 of the Medicines Act 1981, is approximately 2%. The Subcommittee considered that rates of resistance vary, and noted that Erdem et al. (J Glob Infect Dis. 2018:10;129-32) report *E. coli* resistance rates of almost 14% to fosfomycin and about 18% to nitrofurantoin in Turkey.

3.14 The Subcommittee considered that 2% of patients would be intolerant of antibiotics (based on withdrawal rates in clinical trials), and that there would be a small proportion of female patients with poor renal function (glomerular filtration rate [GFR] of less than 60 ml per minute) for whom nitrofurantoin would be contraindicated.

3.15 The Subcommittee considered that there is a need for another treatment option after trimethoprim and nitrofurantoin for multi-drug resistant *E. coli.* The Subcommittee considered that women with uncomplicated UTI due to multi-drug resistant *E. coli* have a high health need.

3.16 The Subcommittee noted that the application is for fosfomycin trometamol (herein referred to as fosfomycin), a broad-spectrum antibiotic which inhibits the first stage of bacterial wall synthesis and is active against both gram-positive and gram-negative bacteria. The Subcommittee considered that although the mechanism of action of fosfomycin is different to that of currently funded agents used for the treatment of uncomplicated UTI, fosfomycin would be used for the same indication.

3.17 The Subcommittee noted that fosfomycin is supplied as powder in a 3g sachet, to be dissolved and taken as a stat dose on an empty stomach. The Subcommittee noted that males would require an additional dose on day four.

3.18 The Subcommittee noted that fosfomycin is not registered for use in New Zealand, however, District Health Board Hospitals have been sourcing fosfomycin under Section 29 of the Medicines Act 1981. The Subcommittee noted that Te Arai BioFarma Ltd submitted an application for registration of fosfomycin to Medsafe in February 2018, and evaluation is underway. The Subcommittee noted that fosfomycin is listed on the Hospital Medicines List (HML) and a proposal for fosfomycin is currently ranked on PHARMACs Options for Investment list (with use restricted to treatment of patients with acute symptomatic bacteriologically-proven lower UTIs and with proven resistance or contraindication to all other oral antibiotics including nitrofurantoin, on the recommendation of an Infectious Disease physician or Clinical Microbiologist).

3.19 The Subcommittee noted the results of the phase III, double-blind, randomised MON-US-03 clinical trial which investigated a single 3 g dose of fosfomycin compared to 7 days of treatment with nitrofurantoin 100 mg twice daily for the first-line treatment of uncomplicated lower UTIs predominantly due to *E. coli* in 749 females (Stein et al. Clin Therap. 1999;21:1864-1872). The Subcommittee noted that the 1-week and 4 to 6-week post-treatment cure rates were 87% and 96% respectively for fosfomycin compared to 81% and 91% respectively for nitrofurantoin, although these did not reach statistical significance.

3.20 The Subcommittee noted that the overall clinical success rate for cure and improvement reported by Stein et al. was 80% in both treatment groups, and that the incidence of adverse events (AEs) was similar with 5.3% of patients in the fosfomycin group and 5.6% in the nitrofurantoin group reporting AEs.

3.21 The Subcommittee noted the results of the double-blind, double-dummy, randomised controlled trial of a single 3 g dose of fosfomycin compared to 7 days of nitrofurantoin 50 mg four times daily used as first-line treatment in 231 patients with symptoms of acute dysuria, stranguria and/or urinary frequency (van Pienbroek et al. Pharm World Sci. 1993;15:257-262). The Subcommittee noted that the day 9 cure rates were 81% for fosfomycin compared to 90% for nitrofurantoin, and that overall efficacy (symptoms and dipslide results) at day 42 were 88% in the fosfomycin group compared to 85% in the nitrofurantoin group although both of these comparisons were not statistically significant.

3.22 The Subcommittee noted van Pienbroek et al. reported a large proportion of patient withdrawals due to AEs occurring by day 9, with 14 of patients withdrawn from the fosfomycin group compared to 4 from the nitrofurantoin group (P=0.015). The Subcommittee noted that AEs were primarily gastrointestinal (GI) and were greater at both day 4 and day 9 in the fosfomycin group than the nitrofurantoin group, but the statistical significance of these results was not reported. The Subcommittee noted that there were no withdrawals due to AEs in the nitrofurantoin group.

3.23 The Subcommittee noted the results of a randomised (2:1) comparative study which investigated a single 3 g dose of fosfomycin compared to 5 days of treatment with trimethoprim 300 mg daily in 300 female patients between 18 and 65 years of age with uncomplicated UTIs predominantly due to *E. coli* (Minassian et al. Int J Antimicrob Agents. 1998;10:39-47). The Subcommittee noted that the authors reported microbiological cure rates at day 7-9 of 83.3% in the fosfomycin group compared to 83% in the trimethoprim group, and infection persisted after treatment in about 17% of patients in each group, although both of these comparisons were not statistically significant. The Subcommittee noted that no safety data was reported.

3.24 The Subcommittee noted the following additional evidence for fosfomycin in the treatment of uncomplicated UTI, including meta-analyses, reviews and international guidelines:

- Falagas et al. J Antimicrob Chemother. 2010;65:1862-77.
- Grigoryan et al. JAMA. 2014;312:1677-84.
- Gupta et al. Clin Infect Dis. 2011;52:e103-20
- Kranz et al. Dtsch Arztebl Int. 2017;114:866-873.
- NICE guideline [NG109]. Urinary tract infection (lower): antimicrobial prescribing.

3.25 The Subcommittee noted that additional clinical trial evidence was submitted in support of this application, however commented that these trials used dose schedules (of trimethoprim, nitrofurantoin or cefalexin) or antibiotics (ciprofloxacin and amoxicillin with clavulanic acid) in the control arm which are not used for standard care in New Zealand. It was also noted that some of the additional evidence pertained to prophylaxis or to the treatment of UTI in pregnancy. The Subcommittee considered that this evidence was not relevant to the indication under assessment.

3.26 The Subcommittee considered that the evidence for fosfomycin for the treatment of uncomplicated UTI was of moderate strength and quality, and that this supported a benefit of fosfomycin for the treatment of multi-drug resistant *E. coli*, however the risks of GI intolerance are likely to be higher than that of nitrofurantoin.

3.27 The Subcommittee considered that women with frequent UTIs and multi-drug resistant *E. coli* infection would benefit the most from treatment with fosfomycin, noting that this would not include pregnant women with UTIs.

3.28 The Subcommittee considered that it was most important for fosfomycin to be used appropriately and that this use would be in patients for whom there is evidence of resistance and where fosfomycin is the most appropriate therapy. Members considered that it would be better to educate prescribers to use fosfomycin appropriately, rather than adding a requirement to the special authority criteria for this product not to be used as a first-line treatment.

3.29 The Subcommittee considered that restricted prescriber access was appropriate for fosfomycin for the treatment of uncomplicated UTI, as wider access would likely result in increased antimicrobial resistance to this broad-spectrum antibiotic which may have an important role in salvage antimicrobial therapy for patients with multi-drug resistant organisms.

3.30 The Subcommittee noted that PHARMAC staff provided evidence from a longitudinal study conducted across 27 hospitals in Spain which monitored the development of antimicrobial resistance to fosfomycin after introduction of this antibiotic for the treatment of UTIs in primary care (Oteo et al. J Antimicrob Chemother. 2010;65:2459-63). The Subcommittee noted that the authors reported an increase in fosfomycin resistance among ESBL producing *E.coli* from 4.4% to 11.4% between 2005 to 2009, and that this increase corresponded to a 340% increase in fosfomycin usage from 1997 to 2009.

3.31 Members considered that the dose form of fosfomycin was appropriate and that the stat dosing offers some advantages over existing treatments. Members considered the convenience of fosfomycin was important and that this would be a suitable oral treatment for use in children also.

3.32 The Subcommittee considered that fosfomycin, if funded, would not create any significant changes in health sector expenditure other than direct treatment costs. The Subcommittee considered that fosfomycin would either not change, or only minimally reduce, the rates of complicated UTI or pyelonephritis requiring hospital admission.

3.33 The Subcommittee considered that the proposed cost of fosfomycin would need to be considered relative to its place in the New Zealand treatment paradigm. The Subcommittee considered that fosfomycin should be used as last line treatment after proven resistance to current therapies, in which case it would be a sequential treatment which would not replace any other antimicrobial agents.

3.34 The Subcommittee considered that New Zealand patients who do not achieve full resolution of their infection from prior therapies (due to antimicrobial resistance) would influence potential costs and savings relating to fosfomycin, and that resistance rates (especially to *E. coli)* should be based on New Zealand data where available.

3.35 The Subcommittee considered that, out of all cases treated with antimicrobial agents, the proportion of uncomplicated UTIs occurring in men (~20% of cases, requiring an additional dose of fosfomycin) and the proportion of complicated UTIs (proportion unknown) would influence the cost of funding fosfomycin due to potential slippage of the Special Authority criteria. Members considered that fosfomycin should have criteria to restrict its use in only the most appropriate treatment settings. Members considered that there would be a risk of slippage even with restriction criteria and optimal clinician education regarding appropriate use of fosfomycin.

4 Salvage IV antibiotics

Application

4.2 The Subcommittee reviewed the following applications for salvage therapy for the treatment of multidrug-resistant organisms:

4.2.1 Fosfomycin (Fomicyt or Fosmicin) for salvage therapy for infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE);

4.2.2 Ceftazidime with avibactam (Zavicefta) for salvage therapy for infections caused by CRE; and

4.2.3 Ceftolozane with tazobactam (Zerbaxa) for significant infections due to multidrug-resistant aerobic Gram-negative organisms, including *Pseudomonas aeruginosa* and extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*.

4.3 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

4.4 The Subcommittee **recommended** that fosfomycin (Fomicyt or Fosmicin) for salvage therapy for infections caused by CRE be deferred due to insufficient evidence for the use of fosfomycin for this indication at this time. The Subcommittee considered that it would welcome a new funding application including further clinical trial data supporting the use of fosfomycin for this indication, once published.

4.5 The Subcommittee **recommended** that ceftazidime with avibactam (Zavicefta) for salvage therapy for infections caused by CRE be funded with a high priority due to the need for a last-line treatment option for this indication and evidence of efficacy. The Subcommittee made this recommendation subject to the following restrictions:

Restricted
Initiation
Clinical microbiologist or infectious disease specialist.
All of the following:

1. Proven resistant micro-organism, based on microbiology report; and
2. Proven infection with carbapenem-resistant *Enterobacteriaceae* (CRE); and
3. Ceftazidime with avibactam will not be used for prophylaxis; and
4. Treatment with colistin is clinically inappropriate.

Note: Where appropriate, treatment with ceftazidime with avibactam should be administered in combination with aztreonam, if available.

4.6 The Subcommittee **recommended** that ceftolozane with tazobactam (Zerbaxa) for significant infections due to multidrug-resistant aerobic Gram-negative organisms,

including *Pseudomonas aeruginosa* and extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, be declined.

4.7 The Subcommittee made the above recommendations because it considered that ceftazidime and avibactam offered the most benefit and was supported by good evidence, that the evidence for fosfomycin was insufficient to provide a benefit, and that the evidence for ceftolozane and tazobactam was not as strong as the evidence for ceftazidime and avibactam. Members considered that ceftazidime with avibactam should reduce the need for new agents against *Ps. aeruginosa*, however, some strains may still require alternative agents and this small number of cases could be managed through the Named Patient Pharmaceutical Assessment (NPPA) process. Members considered that this evolving area of drug-resistant organisms will require ongoing consideration to ensure a range of active agents is available.

Discussion

4.8 The Subcommittee noted that multidrug-resistant organisms (MDROs) pose a serious health concern worldwide due to increasing rates of infection, in part due to increased international travel, and increasing antibiotic resistance. The Subcommittee noted that those at highest risk of contracting an infection with MDROs are immunocompromised or hospitalised patients, such as organ transplant recipients or those in intensive care.

4.9 The Subcommittee noted that the funding applications for salvage therapy for MDROs relate to three distinct indications:

4.9.1 Infection with carbapenem-resistant *Enterobacteriaceae* (CRE)

The Subcommittee noted that CRE (also referred to as carbapenemase-producing *Enterobacteriaceae,* or CPE) is a severe infection often spread by a travelling carrier, but which is becoming increasingly identified in patients who have no travel association. The Subcommittee noted that data on acquired carbapenemases in 2019 from the Environmental Science and Research (ESR) indicates that the majority of CRE in New Zealand is due to *Escherichia coli* and a smaller proportion is due to *Klebsiella pneumoniae* (Data available at: https://surv.esr.cri.nz/antimicrobial/AccqEnterobacteriaceae.php). The Subcommittee noted that standard of care treatment of adults with CRE infection in New Zealand may be with colistin (which is known to be nephrotoxic and which is without an optimal dosing regimen) or with tigecycline (for which the FDA has warned may increase mortality in cases of ventilator-associated pneumonia), usually with either of these agents in combination with another such as aztreonam or aminoglycoside, or a new agent. Members considered that paediatric cases would receive combination treatment using colistin with a new agent. The Subcommittee noted that some CREs (such as New Delhi Metalloproteases, NDM) are completely resistant to therapy and that resistance is spreading. The Subcommittee considered that the available therapies are difficult to use and may not be effective treatment options. The Subcommittee considered that there are limited alternative options for last-line therapy of patients with CRE infection and that there is a high health need for patients with CRE.

4.9.2 Infection with extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae (*EBSL-PE)

The Subcommittee noted that the standard treatment for infections with ESBL-PE is with carbapenem such as meropenem or ertapenem. The Subcommittee noted that all ESBL isolates are currently susceptible to carbapenem and more than 95% susceptible to other agents such as tobramycin, amikacin and cefepime, but there are issues with increasing carbapenem resistance. The Subcommittee considered there is a high health need in patients with ESBL-PE who do not have another treatment option which could otherwise delay, or potentially avoid, the use of carbapenem.

4.9.3 Infection with Pseudomonas aeruginosa (Ps. aeruginosa)

The Subcommittee noted that *Ps. aeruginosa* has multiple different mechanisms of resistance and is inherently resistant to tigecycline. The Subcommittee considered that standard treatment (which may also be required to facilitate lung transplantation) for *Ps. aeruginosa* would consist of the most suitable agent identified from susceptibility data, or dual therapy using cefepime with amikacin or colistin with a carbapenem which have known toxicities. The Subcommittee considered that in some cases there may be no active agent for treatment, such as in the proportion of patients with cystic fibrosis who have *Ps. aeruginosa*. The Subcommittee considered that there is a high health need for patients with *Ps. aeruginosa* infection due to the lack of appropriate treatment for this infection and especially for patients with cystic fibrosis with *Ps. aeruginosa*.

4.10 The Subcommittee noted that the applicants estimate that there would be approximately 5 patient cases per year for fosfomycin, 10 patient cases per year for ceftazidime with avibactam, and 15 patient cases each year for ceftolozane with tazobactam. The Subcommittee considered that it was difficult to estimate the current number of infections per year in New Zealand that are specifically due to CRE, ESBL-PE and *Ps. aeruginosa* respectively. The Subcommittee considered that the number of cases treated with tigecycline and colistin could roughly indicate the number of CRE cases receiving treatment. The Subcommittee considered that the applicant estimates of patient numbers differed between the applications due to an imbalance of available data and clinical information for each of these infections, rather than differences in actual incidence.

4.11 The Subcommittee noted the colonisation data reported by Blakiston et al. (N Z Med J. 2017;130:72-79) which reports almost 50 CPE isolates in 2016 (increased from less than 15 isolates per year during 2009 to 2014) and steady growth in the number of EBSL-PE isolates, rising to between 5,000 and 6,000 cases per year during 2012 to 2014. The Subcommittee considered that the CPE and ESBL-PE colonisation data was suggestive of a sigmoid trend and considered that numbers may stabilise over time, however, the Subcommittee considered that the incidence of severe, life-threatening infections due to MDROs will still occur with increasing frequency in the coming years.

4.12 The Subcommittee noted that, of the relatively new antimicrobial agents with potential use for MDROs, the two which are most important are fosfomycin, for which the oral formulation is currently funded on the Hospital Medicines List (HML) and prescribing is restricted to clinical microbiologist or infectious disease specialists, and ceftaroline, which is mainly active against gram-positive organisms including Methicillin-resistant *Staphylococcus aureus* (MRSA) and is funded in hospitals for multi-resistant organism salvage therapy for patients who have failed

alternative treatments or are intolerant to standard therapies (also restricted to clinical microbiologist or infectious disease specialists).

Fosfomycin (Fomicyt or Fosmicin) for salvage therapy for infections caused by CRE

4.13 The Subcommittee noted that fosfomycin inhibits the first stage of intracellular bacterial wall synthesis by blocking peptidoglycan synthesis. The Subcommittee noted that fosfomycin is widely distributed in the body including to the cerebrospinal fluid, has a half-life of 1.9 to 3.9 hours and is excreted through the kidneys.

4.14 The Subcommittee noted that fosfomycin is supplied as a 2 g, 4 g or 8 g vial of powder for reconstitution and that it is administered by intravenous (IV) infusion. The Subcommittee noted that fosfomycin is not approved by Medsafe, however the oral formulation of fosfomycin is currently listed in the Hospital Medicines List (HML) and is undergoing registration.

4.15 The Subcommittee noted there is limited evidence available for fosfomycin for salvage therapy for infections caused by CRE, and noted the following publications:

- Kaase et al. J Clin Microbiol. 2014;52:1893-7.
- Michalopoulos et al. Clin Microbiol Infect. 2010;16:184-6.
- Pogue et al. J Antibiot (Tokyo). 2013;66:625-7.
- Thaden et al. Virulence. 2017;8:403-416.

4.16 The Subcommittee considered that the minimum inhibitory concentration (MIC) and pharmacokinetic (PK) parameters of fosfomycin need to be better understood in order to facilitate proper use of fosfomycin in salvage therapy.

4.17 The Subcommittee considered that fosfomycin could have a synergistic treatment effect when used with other agents and that the best use of fosfomycin may be against CRE, however, more evidence is needed to understand the agent and its optimal use.

4.18 The Subcommittee considered there were concerns about the rate of development of resistance to fosfomycin, seen in pre-clinical data and in real world clinical practice.

4.19 The Subcommittee considered that the clinical data for fosfomycin for the treatment of CRE infections is very limited and consists of very small case series, and the Subcommittee considered that is evidence base insufficient to assess the potential risks and benefits of fosfomycin for this indication.

4.20 The Subcommittee considered that further clinical trial data would be forthcoming for fosfomycin in the treatment of CRE infection. The Subcommittee considered that it would welcome a new funding application including further clinical trial data supporting the use of fosfomycin for this indication, once published.).

Ceftazidime with avibactam (Zavicefta) for salvage therapy for infections caused by CRE

4.21 The Subcommittee noted that ceftazidime is a third-generation cephalosporin which inhibits bacterial peptidoglycan cell wall synthesis following binding to penicillin

binding proteins, leading to bacterial cell death. The Subcommittee noted that avibactam is a non β-lactam, β-lactamase inhibitor that protects ceftazidime from hydrolysis.

4.22 The Subcommittee noted that ceftazidime and avibactam are supplied as 2 g and 0.5 g of powder (respectively) for reconstitution and are administered by IV infusion The Subcommittee noted that ceftazidime and avibactam are not approved by Medsafe.

4.23 The Subcommittee noted the results of the retrospective, single-site study which compared the outcomes of 109 patients with CRE infections (specifically, *K. pneumoniae*) who received treatment with either ceftazidime and avibactam or an alternative regimen such as carbapenem with aminoglycoside, carbapenem with colistin or other regimen such as aminoglycoside or colistin monotherapy (Shields et al. Antimicrob Agents Chemother. 2017. 61:e00883-17). The Subcommittee noted that the authors report higher rates of clinical success among patients receiving ceftazidime with avibactam compared to those who received a carbapenem with aminoglycoside (*P*=0.04), or compared to colistin (*P*=0.009), or compared to other regimens (*P*=0.004).

4.24 The Subcommittee noted the results from a cohort study of the prospective, multicentre, observational Consortium on Resistance Against Carbapenems in Klebsiella and other Enterobacteriaceae (CRACKLE), which investigated the efficacy of ceftazidime with avibactam compared to colistin in 137 patients with CRE infection (Van Duin et al. Clin Infect Dis. 2018;66:163-171). The Subcommittee noted that the adjusted all-cause hospital mortality at 30 days after starting treatments was 9% with ceftazidime and avibactam compared to 32% with colistin (*P* = 0.001), and there was an adjusted probability of a better outcome of 64% (95% CI: 57% to 71%) with ceftazidime and avibactam. The Subcommittee considered the results of this study show that there is a greater reduction in mortality with ceftazidime with avibactam compared to colistin.

4.25 The Subcommittee also noted the following evidence for ceftazidime and avibactam:

- Alatoom et al. Int J Infect Dis. 2017;62:39-43.
- King et al. Antimicrob Agents Chemother. 2017;61:e00449-17.
- Krapp et al. Int J Antimicrob Agents. 2017;770-773.
- Sader et al. Antimicrob Agent Chemother. 2017;61:e01045-17.
- Shields et al. Clin Infect Dis. 2016. 63:1615-8.

4.26 The Subcommittee noted that the results of the *in vitro* published by Alatoom et al. and Sader et al. report susceptibility of *Ps. aeruginosa* to ceftazidime and avibactam of 94% (29 of 31) and 97% respectively. The Subcommittee considered that the evidence was unable to confirm whether patients with cystic fibrosis who have infection due to *Ps. aeruginosa* would benefit from treatment with ceftazidime and avibactam.

4.27 The Subcommittee considered that ceftazidime with avibactam should be used with aztreonam and considered that this combination treatment would address the

current health need in salvage therapies for the treatment of MDROs, and specifically those infections due to CRE. Members considered that ceftazidime with avibactam should reduce the need for new agents against *Ps. aeruginosa*, however, some strains may still require alternative agents and this small number of cases could be managed through the Named Patient Pharmaceutical Assessment (NPPA) process. The Subcommittee considered that this therapeutic approach would appropriately manage the risk of antimicrobial resistance.

4.28 The Subcommittee considered that the patients who would most likely benefit from ceftazidime with avibactam would be transplant recipients, patients with intensive immunosuppression, those in intensive care and patients who have been admitted to hospital from abroad.

Ceftolozane with tazobactam (Zerbaxa) for significant infections due to MDROs, including Ps. aeruginosa and ESBL-PE

4.29 The Subcommittee noted that ceftolozane is a novel cephalosporin which exerts bactericidal activity through binding to penicillin-binding proteins, resulting in inhibition of bacterial cell-wall synthesis and subsequent cell death. The Subcommittee noted that tazobactam is a beta-lactam structurally related to penicillins.

4.30 The Subcommittee noted that ceftolozane and tazobactam are supplied as 1 g ceftolozane with 0.5 g tazobactam as powder for reconstitution for administration by IV infusion. The Subcommittee noted that ceftolozane and tazobactam are approved by Medsafe for the treatment of adults with complicated intra-abdominal infections (in combination with metronidazole), or for complicated urinary tract infections including pyelonephritis.

4.31 The Subcommittee noted the results of the pooled analysis of two phase III, randomised, double-blind trials investigating ceftolozane and tazobactam in patients with complicated urinary tract infections (ASPECT-cUTI trial) or complicated intra-abdominal infections (ASPECT-cIAI trial) which were reported by Popejoy et al. (J Antimicrob Chemother. 2017. 72:268-72). The Subcommittee noted that the ASPECT-cUTI regimen was 7 days of ceftolozane with tazobactam compared to levofloxacin, and the ASPECT-cIAI regimen was 4-14 days of ceftolozane with tazobactam plus metronidazole compared to meropenem.

4.32 The Subcommittee noted that the pooled analysis included 1,346 patients of which 11% had EBSL-PE at baseline. The Subcommittee noted that reported clinical cure rates for patients with ESBL-PE were 97.4% with ceftolozane and tazobactam (P= 0.006) compared to cure rates of 82.6% for levofloxacin (P=0.011) and 88.5% with meropenem (P>0.005). The Subcommittee considered that the randomised trial data demonstrated high clinical cure rates with ceftolozane and tazobactam treatment for complicated urinary tract infections and intra-abdominal infections caused by ESBL-PE.

4.33 The Subcommittee also noted the following evidence for ceftolozane with tazobactam:

- Alatoom et al. Int J Infect Dis. 2017;62:39-43.
- Escolà-Vergé et al. Infection. 2018;46:461-58.

- Giacobbe et al. Expert Rev Anti Infect Ther. 2018;16:307-320.
- Pfaller et al. J Glob Antimicrob Resist. 2017;10:186-194.
- Shortridge et al. Microb Drug Resist. 2018;24:563-77.
- Solomkin et al. Clin Infect Dis. 2015;60:1462-71.
- Wagenlehner et al. Lancet. 2015;385:1949-56.
- Wi et al. Antimicrob Agents Chemother. 2017;62:e01970-17.

4.34 The Subcommittee considered that ceftolozane and tazobactam was safe and well tolerated. The Subcommittee considered that that the main indication for use of ceftolozane and tazobactam would be against *Ps. Aeruginosa* and that use of this combination of agents may be more suitable than combination treatment using ceftazidime with avibactam against this organism.

General

4.35 The Subcommittee considered it is difficult to conduct high-quality research investigating salvage therapy for MDROs due to the challenges associated with small patient numbers, treatment timeframes and participant non-acceptance of standard therapies. The Subcommittee considered that it is unlikely to expect that randomised controlled trials would be performed to investigate salvage IV therapies.

4.36 The Subcommittee considered that ceftazidime and avibactam offered the most benefit and was supported by good evidence, that the evidence for fosfomycin was insufficient to provide a benefit, and that the evidence for ceftolozane and tazobactam was not as strong as the evidence for ceftazidime and avibactam.

4.37 The Subcommittee considered that the number of cases requiring salvage therapy will double over the next 10 years based on the sigmoid trend in the colonisation data. The Subcommittee considered that, in patients with cystic fibrosis, there is insufficient evidence to support the use of any of these agents (fosfomycin, ceftazidime and avibactam, or ceftolozane and tazobactam) for salvage therapy for MDROs, and particularly for infections due to *Ps. aeruginosa*.

4.38 The Subcommittee considered that funding of any of these agents (fosfomycin, ceftazidime and avibactam, or ceftolozane and tazobactam) would not create significant changes in health-sector expenditure other than for direct treatment costs, however, improved outcomes in septic patients may reduce the length of inpatient hospital stays. The Subcommittee considered that if ceftazidime and avibactam were funded, this treatment (in combination with aztreonam) would replace colistin and tigecycline, avoiding the toxicities associated with those agents. The Subcommittee considered that funding of ceftazidime and avibactam may help to avoid carbapenem use, although initial estimates of costs of ceftazidime and avibactam are about six times that of meropenem.

4.39 The Subcommittee noted that the dosing regimen of these agents and combinations would influence the treatment cost and considered that the dosing regimens to be used should be based clinical trial data including pharmacokinetic data of the agents used. Specifically, the Subcommittee considered that the dosing of fosfomycin was

estimated incorrectly and this should be addressed if the application is reviewed again if further clinical trial data is received.

5 Non-occupational post-exposure prophylaxis (nPEP) in unknown HIV status and widening of prescriber type

Application

5.2 The Subcommittee reviewed an application from the New Zealand Aids Foundation which sought to:

5.2.1 Expand eligibility criteria for non-occupational post-exposure prophylaxis (nPEP) of HIV to include receptive anal sex with a person of unknown HIV serostatus which was condomless or where a condom failed.

5.2.2 Expand PEP prescribers to include sexual health physicians, nurse practitioners in a sexual health clinic and GPs who have undergone accredited PEP and PrEP training. PEP and PrEP training could then be co-delivered efficiently.

5.3 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

5.4 The Subcommittee **recommended** that the antiretroviral Special Authority criteria for nPEP be amended, to closer align with the UK and ASHM guideline risk assessment tool, with a high priority to include:

a) for source partners with a known positive HIV status (viral load greater than 200 copies/ml): receptive and insertive anal sex or receptive vaginal sex;

b) for source partners with an unknown HIV status to include; receptive anal sex with a person from a high HIV prevalence country or high HIV prevalence risk group.

5.5 The Subcommittee **recommended** that initiating Special Authority for PrEP and nPEP be widened to include sexual health specialist, infectious disease specialists and vocationally registered general practitioner or nurse practitioner.

5.6 The Subcommittee **recommended** that the Special Authority criteria for antiretrovals be separated into two groups:

a) Confirmed HIV, prevention of maternal transmission and percutaneous exposure which should still be limited to named specialists;

b) PrEP and PEP where sexual health specialists, infectious disease specialists, vocationally registered general practitioners or nurse practitioners can initiate patients.

Discussion

5.7 The Subcommittee noted that nPEP is recommended, based on risk of transmissible exposure, to be commenced within 72 hours and is typically a two or three drug regimen that is continued for 28 days. Members noted that two drug

regimens include emtricitabine/tenofovir disoproxil or tenofovir disoproxil with lamivudine; three drug regimens include dolutegravir, raltegravir or rilpivirine in addition to the two drug regimen.

5.8 The Subcommittee noted that the current nPEP criteria is not in-line with the latest evidence of transmission of HIV noting that most transmission is driven by people that are unaware that they have HIV. (Saxton et al, 2015A. HIV prevention todayNZMJ; 128(1426): 8-15) The Subcommittee noted that when the criteria were developed they were based on limiting the patient group to a risk greater than 1 in 300 and this took into account a high drug cost and was based on the current percutaneous occupational risk. Members noted that PHARMAC has recently competed the antiretroviral market which included significant price reductions for emtricitabine with tenofovir disoproxil.

5.9 The Subcommittee noted that current treatment paradigm now considers that HIV positive patients who are on treatment and have an undetectable viral load for six months cannot transmit the virus, so treating patients only with known HIV status is no longer relevant.

5.10 The Subcommittee considered the it would be highly unlikely for there to be a definitive placebo-controlled trial conducted in the setting of nPEP and current treatment recommendations are based on risk of transmission calculated from known case reports, mother-to-child transmission studies and occupational exposure data. The Subcommittee noted that current international practice (such as the Australasian Society for HIV (ASHM)) is to calculate risk of the patient being infected by multiplying the exposure type by the likelihood that the source has transmissible HIV. Members noted ASHM had performed a significant review of the literature in 2016 which was published on its website: https://www.ashm.org.au/HIV/PEP/PEP_Literature_Review_2016.PDF

5.11 The Subcommittee noted that treatment recommendations for jurisdictions outside of New Zealand varies and many use a risk greater than 1 in 1000 as a basis of recommending treatment. Members noted that, in Australia for example, the funding of nPEP is not via the Pharmaceutical Benefits Scheme (PBS) as the cost of the medicine is funded by State and territory Departments of Health. The treating clinician will consider the ASHM guidelines and consider the benefits of treatment compared with the risk of harm.

5.12 Members considered that the landscape has changed: that HIV medication is much more well-tolerated and affordable and that it is reasonable to consider a risk of 1:1000, rather than 1:300, In line with international literature reviews and guidelines. Members considered that an acceptable risk to treat in New Zealand was 1 in 1000 which included in HIV positive or unknown viral load partners who had receptive and insertive anal sex or receptive vaginal sex, but this did not include insertive vaginal sex. For a partner with unknown HIV status, this included receptive anal sex only.

5.13 The Subcommittee noted the current prescriber restrictions for nPEP and considered that access to treatment can be inequitable when there is poor access to a named antiretroviral specialists. Members considered that in Queenstown, for example, the nearest hospital is 4 hour drive away and there are no named antiretroviral specialists. Members also noted that the current criteria has components open to interpretation and considered it is timely for this Subcommittee to review the criteria given that PrEP has been funded since January 2018.

5.14 The Subcommittee considered that since funding PrEP it has become quite evident that the nPEP and PrEP prescriber access to antiretrovirals should be widened. There needs to be better access for prescribers who treat vulnerable patients in the community and the same barriers to access (for HIV chronic treatment for example) need not be in place. The Subcommittee also considered that similar prescribers should be able to provide both nPEP and PrEP and that it is important (for PrEP) that prescribers acknowledge that they have sought training to be competent in the risks and benefits of these treatments in these patients groups.

5.15 The Subcommittee recommended changes to the nPEP Special Authority criteria to widen the prescriber access and allow treatment for patients where there is a risk of 1 in 1000 or greater (additions in bold, deletions in strikethrough):

> Initial application — (post-exposure prophylaxis following non-occupational exposure to HIV) only from a ~~named specialist~~ **sexual health specialist, infectious disease specialist, vocationally registered general practitioner or nurse practitioner**. Approvals valid for 4 weeks for applications meeting the following criteria:
> Both:
> 1 Treatment course to be initiated within 72 hours post exposure; and
> 2 Any of the following:
> 2.1 Patient has had unprotected receptive anal intercourse with a known HIV positive person **with an unknown or detectable viral load greater than 200 copies per ml**; or
> **2.2 Patient has had unprotected insertive anal intercourse with a known HIV positive person with an unknown or detectable viral load greater than 200 copies per ml; or**
> **2.3 Patient has had unprotected receptive vaginal sex with a known HIV positive person with an unknown or detectable viral load greater than 200 copies per ml; or**
> **2.4 Patient has had unprotected receptive anal intercourse with a person from a high prevalence country or risk group whose HIV status is unknown; or**
> 2.~~2~~**5** Patient has shared intravenous injecting equipment with a known HIV positive person; or
> 2.~~3~~**6** Patient has had non-consensual intercourse and the clinician considers that the risk assessment indicates prophylaxis is required.
>
> **Notes: For the purpose of 2.3 above, 'unprotected receptive vaginal sex' refers to intercourse between an HIV positive male and a HIV negative female**
>
> Renewal — (second or subsequent post-exposure prophylaxis) only from a ~~named specialist~~ **sexual health specialist, infectious disease specialist, vocationally registered general practitioner or nurse practitioner**. Approvals valid for 4 weeks for applications meeting the following criteria:
> Both:
> 1 Treatment course to be initiated within 72 hours post exposure; and
> 2 Any of the following:
> 2.1 Patient has had unprotected receptive anal intercourse with a known HIV positive person **with an unknown or detectable viral load greater than 200 copies per ml**; or
> **2.2 Patient has had unprotected insertive anal intercourse with a known HIV positive person with an unknown or detectable viral load greater than 200 copies per ml; or**
> **2.3 Patient has had unprotected receptive vaginal sex with a known HIV positive person with an unknown or detectable viral load greater than 200 copies per ml; or**
> **2.4 Patient has had unprotected receptive anal intercourse with a person from a high prevalence country or risk group and their HIV status is unknown; or**
> 2.~~2~~**5** Patient has shared intravenous injecting equipment with a known HIV positive person; or

2.~~3~~**6** Patient has had non-consensual intercourse and the clinician considers that the risk assessment indicates prophylaxis is required.

Notes: For the purpose of 2.3 above, 'unprotected receptive vaginal sex' refers to intercourse between an HIV positive male and a HIV negative female

5.16 The Subcommittee considered the request for the availability of starter packs in emergency departments and sexual health clinics for patients starting nPEP; noting that treatment needs to start within 72 hours of exposure. The Subcommittee considered that some hospitals already provide emtricitabine with tenofovir disoproxil as a starter pack dispensed by their hospital pharmacy. Members noted that for emergency use, in a community setting, a practitioners supply order, would normally be used as a mechanism however this is not possible with a pharmaceutical that has a restriction.

5.17 The Subcommittee recommended changes to the PrEP Special Authority criteria to widen the prescriber access to initiations and also cover the testing and considerations required for community initiations of this treatment (additions in bold, deletions in strikethrough):

Initial application only from a ~~named specialist or medical practitioner on the recommendation of a named specialist~~ **sexual health specialist, infectious disease specialist, vocationally registered general practitioner or nurse practitioner**.
Approvals valid for 3 months for applications meeting the following criteria:

~~Both~~ **All of the following**:

1. **Applicant has an up to date knowledge of the safety issues and is competent to prescribe pre-exposure prophylaxis (refer to local health pathways or https://ashm.org.au/HIV/PrEP/ for training materials); and**
2. **Patient has undergone testing for HIV, syphilis, Hep B if not immune and a full STI screen in the previous two weeks; and**
3. **Patient has had renal function testing (creatinine, phosphate and urine protein/creatinine ratio) within the last 3 months and is not contraindicated for treatment; and**
4. **Patient has received advice regarding the reduction of risk of HIV and sexually transmitted infections and how to reduce those risks; and**
5. Patient has tested HIV negative **and is not at risk of HIV seroconversion**; and
6. Either:
   - 6.1. All of the following:
     - 6.1.1. Patient is male or transgender; and
     - 6.1.2. Patient has sex with men; and
     - 6.1.3. Patient is likely to have multiple episodes of condomless anal intercourse in the next 3 months; and
     - 6.1.4. Any of the following:
       - 6.1.4.1. Patient has had at least one episode of condomless receptive anal intercourse with one or more casual male partners in the last 3 months; or
       - 6.1.4.2. A diagnosis of rectal chlamydia, rectal gonorrhoea, or infectious syphilis within the last 3 months; or
       - 6.1.4.3. Patient has used methamphetamine in the last three months; or
   - 6.2. All of the following:
     - 6.2.1. Patient has a regular partner who has HIV infection; and
     - 6.2.2. Partner is either not on treatment or has a detectable viral load; and
     - 6.2.3. Condoms have not been consistently used.

Renewal from any relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:

1. Applicant has an up to date knowledge of the safety issues and is competent to prescribe pre-exposure prophylaxis **(refer to local health pathways or https://ashm.org.au/HIV/PrEP/ for training materials)**; and

2. Patient has undergone testing for HIV, syphilis, **Hep B if not immune** and a full STI screen in the previous two weeks; and
3. Patient has had renal function testing (creatinine, phosphate and urine protein/creatinine ratio) within the last 12 months **and is not contraindicated for treatment**; and
4. Patient has received advice regarding the reduction of risk of HIV and sexually transmitted infections and how to reduce those risks; and
5. Patient has tested HIV negative **and is not at risk of HIV seroconversion**; and
6. Either:
    - 6.1. All of the following:
        - 6.1.1. Patient is male or transgender; and
        - 6.1.2. Patient has sex with men; and
        - 6.1.3. Patient is likely to have multiple episodes of condomless anal intercourse in the next 3 months; and
        - 6.1.4. Any of the following:
            - 6.1.4.1. Patient has had at least one episode of condomless receptive anal intercourse with one or more casual male partners in the last 3 months; or
            - 6.1.4.2. A diagnosis of rectal chlamydia, rectal gonorrhoea, or infectious syphilis within the last 3 months; or
            - 6.1.4.3. Patient has used methamphetamine in the last three months; or
    - 6.2. All of the following:
        - 6.2.1. Patient has a regular partner who has HIV infection; and
        - 6.2.2. Partner is either not on treatment or has a detectable viral load; and
        - 6.2.3. Condoms have not been consistently used.

6 Oseltamivir for treatment and prophylaxis of influenza in Long Term Care Facilities (LTCFs)

Application

6.2 The Subcommittee reviewed an application from the Ministry of Health to fund oseltamivir for the treatment and prophylaxis of patients in long term care facilities (LTCFs) during influenza outbreaks within the facility.

6.3 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

6.4 The Subcommittee recommended that the application for oseltamivir for the treatment and prophylaxis of patients in long term care facilities (LTCFs) during influenza outbreaks within the facility be declined due to insufficient evidence of benefit in this patient group and treatment setting.

Discussion

6.5 The Subcommittee noted that in February 2013 and May 2013 PTAC considered the role of neuraminidase inhibitors (oseltamivir and zanamivir) including use in high risk patients. PTAC considered that the benefits of neuraminidase inhibitors were limited, and that there is insufficient evidence of benefit (beyond a reduction of time to alleviation of symptoms) to recommend wider funding. PTAC had recommended that funding be limiting to hospitalised patients who are likely to have more severe forms of influenza and/or are at high risk of influenza complications.

6.6 The Subcommittee noted that between 2015 and 2017 there was an average of 11 outbreaks of influenza in LTCFs per year reported by ESR, with an average of 240 cases per year associated with these outbreaks. The Subcommittee noted applicant estimations that 649 residents would be treated per annum if oseltamivir was funded in this treatment setting. Members considered that if funding was included for this patient group there would likely be much higher patient numbers.

6.7 The Subcommittee considered that patients in LTCFs have a high health need as they are more frail that similarly aged patients in the community. Members also considered that influenza vaccination rates are high, however the protective effect of the vaccine is likely to be less than that seen in community dwelling elderly of similar age. Members also noted that due to communal living they are at risk of influenza spread within the facility. Members considered that the application did not consider whether or not a LTCF practises disease control and prevention during outbreaks, or whether prophylaxis would be based on a patient's immunisation status.

6.8 The Subcommittee considered whether Maori or Pacific Island people are at an increased risk of complication in nursing homes due to influenza infection. Members noted that Maori and Pacific people are less likely to dwell with in LTCF. In 2013, 32,000 people lived in LTCF for older people across 822 facilities; 68.1% of those were female and 92.5% were of European ethnicity (Maori 3.3%, Pacific Island 1.5%), 75% of the residents were over 80 years of age. The Subcommittee considered that Maori and Pacific people are less represented in LTCF population.

6.9 The Subcommittee noted that the purpose of making oseltamivir available for treatment and prophylaxis is to reduce the morbidity and mortality from seasonal influenza. Members noted that vaccination, infection control activities (e.g. isolation and prevention of cross infection) and GP care with provision of antibiotics for influenza complications are available within LTCFs. Members noted that oseltamivir is the current preferred antiviral option recommended in guidelines from overseas jurisdictions' review of the literature.

6.10 The Subcommittee noted the following publications:

- Peters et al. Journal of the American Geriatrics Society, 2001; 49(8): 1025-1031.
- Van der Sande et al. Emerging themes in epidemiology, 2014; 11(1): 13.
- Mertz et al. BMJ, 2013; 347.
- Jefferson et al. Cochrane Database of Systematic Reviews, 2014; CD008965.
- Yip et al. Public health, 2018; 162: 98-103.
- Bowles et al. Journal of the American Geriatrics Society, 2002; 50(4): 608-616.
- Ye et al. BMJ open, 2016; 6(7): e011686.
- Monto et al. Clinical Infectious Diseases, 2004; 39(4): 459-464.
- Lee et al. New England Journal of Medicine, 2010; 362(23): 2166-2174.

- Dobson et al. Lancet. 2015; 9979(385): 1729-37

- Muthuri et al. The Lancet Respiratory medicine. 2014; 2(5): 395-404.

4.10 The Subcommittee noted international guidelines and evidence review provided by the applicant including:

- Guidance for practitioners on the use of antiviral drugs to control influenza outbreaks in long-term care facilities in Canada. Can J Infect Dis Med Microbiol. 2015; 26(1): e1–e4.

- Guidelines for the Prevention, Control and Public Health Management of Influenza Outbreaks in Residential Care Facilities in Australia. CDNA, Editor. 2017: Australia

- Expert opinion on neuraminidase inhibitors for the prevention and treatment of influenza–review of recent systematic reviews and meta-analyses. European Centre for Disease Prevention and Control.

- World Health Organization, Prevention and control of outbreaks of seasonal influenza in long-term care facilities: a review of the evidence and best-practice guidance. WHO Regional Office for Europe, 2017.

6.11 The Subcommittee noted that, from a treatment perspective, there is very little evidence of a benefit of treatment in the elderly population. The only Randomised Controlled Trials (RCTs) that have been undertaken specifically in the elderly were WV15819, WV15876 and WV15978 which had been considered by PTAC in 2013. Members noted that these studies had not shown a significant difference between oseltamivir and placebo with respect to time to alleviate symptoms or hospitalisations.

6.12 The Subcommittee noted that, from a prophylaxis perspective, there are no level 1 (RCT) studies. The only RCT provided in this setting considered Dutch nursing homes during four influenza seasons between 2009-2013. (Van der Sande et al. Emerging themes in Epidemiology, 2014; 11:13) Members noted that of the 42 nursing homes recruited 15 outbreaks were included in the analysis which failed to find statistic significant of a protective effect, Members noted that the low outbreak numbers negatively impacted the power of the study. Members also noted that there were logistic challenges in ensuring the timely administration of prophylaxis. The Subcommittee considered this was relevant to the New Zealand setting and questioned whether prophylaxis could be given in a timely fashion if oseltamivir was funded in this patient group.

6.13 The Subcommittee noted a cluster RCT (Booy et al. PLoS one, 2012; 7(10): e46509) which considered 16 aged care facilities randomly assigned treatment “T” (oseltamivir treatment 75 mg twice daily for five days) or treatment and prophylaxis “T&P” (oseltamivir 75 mg once daily for 10 days), the primary outcome being the attack rate of influenza like illness. The Subcommittee noted that the confirmed influenza case on residents between the two arms was not significant (p=0.4). There was a significant reduction in mean duration of outbreaks (T= 24 days, T&P=11 days p=0.04). There was a non-significant reduction in deaths, hospitalisations and pneumonia in the T&P group. The Subcommittee noted the low power of the study which was a result of low number of influenza outbreaks during the reported period.

6.14 The Subcommittee considered Singh et al. Infection Control and Hospital Epidemiology, 2018; 39(8): 955-60. A retrospective observation study which analysed 53 H3N2 out breaks during 2014-2015 in LTCFs in Manitoba, Canada. This study looked at secondary attack rate in relationship to timing of oseltamivir chemoprophylaxis. The study observed that delay of oseltamivir was associated with increased odds of infection on both univariate ($P<0.0001$) and multivariable analyses ($p<0.001$)

6.15 The Subcommittee considered that there is no RCT evidence that hospitalisation rates would be reduced given the lack of level 1 evidence for efficacy of treatment in the elderly and the lack evidence for efficacy of prophylaxis in LTCF. The Subcommittee further considered that all other (non-RCT) evidence is noncontrolled observational data. This data suggests that LTCF outbreaks may terminate quicker if prophylaxis is provided in a timely fashion, but does not address the hard endpoint of morbidity, hospitalisation or deaths.

6.16 The Subcommittee concluded that the only rationale for funding in this setting would be on the basis that international guidelines on LTCF antiviral treatments have recommended providing treatment and prophylaxis despite the poor evidence base. The Subcommittee noted that many statements in the guidelines that recommend treatment do not cite any supporting evidence or acknowledge that the evidence base is light and more studies are required. Members considered that in New Zealand, medicines of modest benefit with a poor evidence base that have a significant budget impact are difficult to justify funding ahead of better investments.