Feedback from operational stakeholders who manage or respond to outbreaks is that they are often too busy to review literature or obtain relevant background information to assist them with acute response. Unlike a traditional analytical outbreak investigation report, ***Watching Briefs*** *are intended as a rapid resource for public health or other first responders in the field on topical, serious or current outbreaks, and provide a digest of relevant information including key features of an outbreak, comparison with past outbreaks and a literature review. They can be completed by responders to an outbreak, or by anyone interested in or following an outbreak using public or open source data, including news reports.*

Watching brief	
Title	Outbreak of an extensively resistant strain of *Pseudomonas aeruginosa* in the United States
Authors	Rosalie Chen and Ashley Quigley
Date of first report of the outbreak	In November 2022, the California Department of Public Health reported that the United States (US) Centers for Disease Control and Prevention (CDC) was requesting information regarding cases via their Epidemic Information Exchange network [1]. On 20-Jan-2023, the American Association of Ophthalmology issued a statement advising that the CDC was investigating the outbreak [2].
Disease or outbreak	The current outbreak is caused by *Pseudomonas aeruginosa*, a Gram-negative, facultative aerobic, rod-shaped bacterium [3]. The outbreak strain is a Verona Integron-mediated Metallo-β-lactamase (VIM)- and Guiana-Extended Spectrum-β-Lactamase (GES)- producing carbapenem-resistant *Pseudomonas aeruginosa* (VIM-GES-CRPA) [4].
Origin (*country, city, region*)	Los Angeles County, California, US
Suspected Source (specify food source, zoonotic or human origin or other)	The source of the VIM-GES-CRPA outbreak is suspected to be 'Ezricare Artificial Tears' eyedrops [4]. These eyedrops (marketed also under the brand name 'Delsam Pharma'), are an over-the-counter (OTC) preservative-free eyedrop, manufactured in Chennai, India, by Global Pharma Healthcare, and sold in popular stores including Walmart and Amazon [5,6].

	Laboratory testing by the CDC of opened eyedrop bottles identified the presence of VIM-GES-CRPA matching the outbreak strain, with ongoing testing to determine whether bottles were contaminated during manufacturing or after opening [4]. A nationwide recall of the eyedrops was issued on 2-Feb-2023 [7]. On 21-Feb-2023, another OTC product, 'Delsam Pharma's Artificial Eye Ointment' was also recalled due to potential contamination [7].
Date of outbreak beginning	The earliest date of specimen collection was 17-May-2022 [8]. The delay between outbreak onset and first official report may have been due to the sporadic, widespread nature of cases.
Date outbreak declared over	Ongoing
Affected countries & regions	As of 14-Mar-2023, 16 US states have reported cases: California, Colorado, Connecticut, Florida, Illinois, North Carolina, New Jersey, New Mexico, New York, Nevada, Pennsylvania, South Dakota, Texas, Utah, Washington, Wisconsin [4].
Number of cases (specify at what date if ongoing)	68 cases as of 14-Mar-2023 [4].
Clinical features	*P. aeruginosa* eye infections can cause [9]: • Discomfort, pain • Redness • Mucopurulent discharge • Photophobia • Conjunctival, eyelid or corneal oedema • Reduced visual acuity Clinical features of *P. aeruginosa* infection in other tissues include [10]: • Fever • Lymphadenopathy • Joint pain • Systemic inflammation • Maculopapular pruritic rash

	• Diarrhoea • Wound/burn infections (local tenderness, swelling, purulent discharge) • Lung infections (pneumonia, severe coughing, congestion) • Ear infections (otalgia, otorrhea)
Mode of transmission (dominant mode and other documented modes)	*P. aeruginosa* is an opportunistic pathogen commonly found in the environment, including in soil and water [11]. Nosocomial infections are common, with *P. aeruginosa* causing an estimated 7.1-7.3% of healthcare-associated infections and 23% of ICU-acquired infections [12]. *P. aeruginosa* causes 10% of all ventilator-associated pneumonia and catheter-associated urinary tract infections (UTIs) [12]. Transmission may occur via direct contact with contaminated hands, surfaces, or equipment, or ingestion of contaminated water or food, particularly raw vegetables [13,14]. Aerosol transmission is also possible [11]. Ocular infections may cause systematic effects, as bacteria can enter the nasal cavity via the tear ducts, and then disseminate to the lungs and other sites via the bloodstream [15].
Demographics of cases	Limited demographic information is available. However, it is known that 25 cases occurred across five nursing homes in Connecticut, and six cases occurred in Davis County, Utah [16]. Three cases have died, including a man from Washington [4,16]. Demographic information is lacking for the remaining cases.
Case fatality rate	During the current outbreak, the case fatality rate is 4.41% [4].
Complications	*P. aeruginosa* eye infections can lead rapidly to permanent vision loss or blindness, due to scarring following corneal ulceration or severe inflammation [17,18]. *P. aeruginosa* keratitis is challenging to manage, with poor prognosis if untreated [17]. Progression to endophthalmitis is rare, but visual outcomes are very poor, potentially requiring evisceration or enucleation [18,19]. During the current outbreak, at least eight cases experienced permanent vision loss, and four cases required enucleation [16].

	Systemic *P. aeruginosa* infections can cause respiratory complications, UTIs, endocarditis, meningitis, septicaemia, and death [20]. A 30-day mortality rate of 33.8-36.7% has been reported for patients with *P. aeruginosa* bacteraemia [21,22].
Available prevention	Several measures assist with preventing *P. aeruginosa* infections and reducing nosocomial transmission risk [13,23]: • Maintaining hand hygiene • Environmental cleaning • Sterilising shared medical equipment • Ensuring water quality and cleanliness of water reservoirs • Performing quality assurance of medical products
Available treatment	*P. aeruginosa* is often resistant to many antibiotics, including carbapenems [3]. Some carbapenem-resistant strains produce carbapenemases, with VIM and GES being respectively the first and second most common *P. aeruginosa* carbapenemases globally [24,25]. Due to this widespread carbapenem resistance, combination therapy is commonly used to increase treatment efficacy [26]. However, during this outbreak, susceptibility testing indicated that VIM-GES-CRPA isolates were resistant to many antimicrobials and combination drugs, though three isolates demonstrated susceptibility to cefiderocol [4]**.** Cefiderocol is a cephalosporin that overcomes Gram-negative resistance mechanisms by acting as a siderophore to transport across the outer cell membrane, after which it inhibits cell wall synthesis [27].
Comparison with past outbreaks	This is the first VIM-GES-CRPA outbreak reported in the US and globally; no other confirmed or suspected outbreaks have been documented. However, several genomic analysis studies have identified the co-expression of VIM and GES genes, of differing variants, in isolated cases in several countries [28-33] (Table 1).

Table 1. Studies that have identified *P. aeruginosa* isolates co-harbouring VIM and GES genes

Author	Collection Period	Country	Study type	Number & source of isolates with both VIM & GES	VIM variant detected	GES variant detected
Pasteran et al. (2005) [28]	2002	Argentina	Case report	One isolate, from a 7-month-old hospital patient	VIM-11	GES-5
Castillo-Vera et al. (2012) [29]	2004	Mexico	Retrospective cohort	Seven of 14 isolates from intensive care patients had GES-5 with VIM-2 and/or VIM-11	VIM-11, VIM-2	GES-5
Ríos et al. (2018) [30]	2012	Peru	Case report	One isolate, from an 83-year-old hospitalised woman	VIM-2	GES-1
Ferjani et al. (2022) [31]	2014-2017	Tunisia	Retrospective cohort	One of 35 isolates from hospitalised patients	VIM-11	GES-5
Moubareck et al. (2019) [32]	2015-2016	United Arab Emirates	Prospective cohort	5.4% of 37 isolates from patients across 4 hospitals	VIM-43, VIM-2	GES-5, GES-9
Ejaz et al. (2022) [33]	Not stated	Saudi Arabia	Prospective cohort	Three of 71 isolates from hospitalised patients	Not stated	Not stated

A similar outbreak, caused by Verona integron-encoded metallo-β-lactamase–producing carbapenem-resistant *Pseudomonas aeruginosa* (VIM-CRPA), occurred in the US in 2019, and was linked to invasive procedures performed in Tijuana, Mexico. By 11-Feb-2019, 20 VIM-CRPA cases were identified across nine states [34]. Of 17 cases with available data, 14 were female, aged 29-62 years [34]. Fifteen cases had surgery at Grand View Hospital in Tijuana [34]. Thirteen were hospitalised, most with surgical site infection, and one death occurred, in a patient with bacteraemia and several comorbidities [34]. Subsequent investigations identified poor facility infection control practices, including failure to properly sterilise equipment [35].

Although this previous outbreak was caused by a different *P. aeruginosa* strain, it demonstrates the bacteria's propensity to cause nosocomial infections. In contrast, the current outbreak is associated with eyedrop use, rather than surgery in a healthcare setting. Though

	limited information is available, current case demographics may be quite different compared to the previous outbreak due to the source of this infection.
Unusual features	This outbreak is the first detection of a CRPA strain harbouring both VIM and GES genes in the US. Genomic analyses demonstrate that such a combination is rare; one review study in the Arab region found that co-expression of either VIM or GES genes often occurs with genes for oxacillinases (OXA) instead [36]. The large number of cases is therefore alarming, as carbapenemase-producing strains are still uncommon in the US (though their prevalence may be under-reported) [24]. The association of cases with eyedrops, rather than nosocomial infection in healthcare settings, is also unusual. The lack of an obvious common transmission event could have hindered investigation efforts, as cases occurred over several months, across different locations, and with various clinical presentations [16]. This may explain the delay in official reporting and subsequent recall initiation, by which time 55 cases and one death had already occurred [7]. This outbreak also demonstrates the difficulty in identifying and linking cases linked to OTC medical products, which is concerning given the virulence of VIM-GES-CRPA.
Critical analysis	Antimicrobial resistance (AMR) is growing rapidly worldwide [37], with alarming healthcare implications. AMR occurs when pathogens adapt to no longer respond to previously effective medications [38]. This causes serious illnesses that require lengthier, costlier and more intensive care to treat, with vulnerable populations (e.g. the very young, the elderly) especially likely to experience increased morbidity and mortality [39,40]. The emergence of increasingly resistant pathogens, such as dual- (or even multi-) carbapenemase-producing bacteria, like VIM-GES-CRPA during the current outbreak, is therefore extremely concerning. Unfortunately, there is limited data regarding global VIM-GES-CRPA prevalence, and although isolated confirmed cases have occurred in several countries, there is likely underreporting [28-33]. Ezricare eyedrops were marketed in the US [41], however, the outbreak source could be certain eyedrop ingredients or manufacturing equipment.

	Therefore, additional VIM-GES-CRPA cases could occur elsewhere, as Global Pharma Healthcare exports to over 30 countries [42]. Increased surveillance is thus urgently needed, yet is often ignored and under-resourced [43]. The current VIM-GES-CRPA outbreak highlights the challenges of identifying novel strains of resistant pathogens, linking cases, and pinpointing outbreak sources. There is therefore a need for surveillance systems that can identify novel or concerning resistant pathogens, gather data on antimicrobial use, provide early disease warnings, and support outbreak management. Efforts to establish a global AMR surveillance system have only occurred relatively recently, with the World Health Organization (WHO) launching the Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2015 [44]. By the end of 2021, 109 countries and two territories and areas were enrolled in GLASS for AMR surveillance, with only 33 of these also involved in antimicrobial consumption surveillance [44]. Thus, greater efforts to encourage enrolment by nations and expand both antimicrobial resistance and consumption surveillance are required. Surveillance is also an important biosecurity consideration, as knowledge of AMR mechanisms could be used in genetic engineering of pathogens for biocrime and bioterrorism [45]. Genomic and disease surveillance are therefore critical for monitoring AMR and ensuring public health. Improving laboratory diagnostic capacity is another crucial aspect of antimicrobial stewardship and AMR surveillance. Timely, accurate diagnoses help guide clinical decision-making and optimise the use of existing medications [43]. Whole-genome sequencing was used in the current outbreak to show that cases were closely related, with 37 linked to four healthcare facilities, and assisted with epidemiological investigations [4]. However, not all laboratories have sufficient resources for susceptibility testing or whole-genome sequencing [46], particularly in lower-resource settings. Thus, some cases during the current VIM-GES-CRPA outbreak may not have been captured by laboratory surveillance. Efforts to combat AMR must therefore improve access to confirmatory testing services and ensure appropriate testing policies and resources.

	Urgent action is needed to address AMR. This includes expanding disease surveillance, enhancing rapid pathogen detection and identification measures, and improving guidance on clinical prevention and management. This outbreak should provide yet another warning for public health authorities and governments that cross-disciplinary, co-ordinated efforts are needed to bolster AMR surveillance globally and address the multi-faceted causes that have contributed to its spread.
Key questions	• How can public awareness of AMR be improved within communities and industries? • How can genomic and disease surveillance systems be used more effectively in conjunction to provide early warning of AMR in pathogens and cases of disease? • How can laboratory testing be strengthened to ensure rapid pathogen identification with efficient, equitable use of resources? • How might laboratory testing referral pathways be strengthened to encourage, and improve access to, confirmatory testing? • How can countries avoid importing novel strains of resistant pathogens (e.g. in medical products, food, livestock, etc.)? • How can the identification and linkage of cases during outbreaks associated with OTC products be improved? • Should the purchase and use of OTC products be regulated more stringently? How? • Are current quality assurance measures for OTC products sufficient? How might they be strengthened?

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