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Review

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Inter- and intra-bacterial strain diversity remains the "elephant in the (living) room"

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Acinetobacter baumannii is an opportunistic Gram-negative bacterial pathogen responsible for severe nosocomial infections worldwide. Resistance to last-resort antibiotics causes *A. baumannii* to be ranked as a top priority for the research and development of new antibiotics by the WHO and an urgent threat to public health by the CDC. It is also a member of the ESKAPE group comprising the most problematic antibiotic-resistant nosocomial pathogens. Resistance towards desiccation, disinfectants, reactive oxygen species, and the host immune system helps *A. baumannii* thrive in hospital settings and infect individuals compromised by lines, tubes, and indwelling devices. *A. baumannii* displays extensive genomic heterogeneity, yet recent studies show that this level of plasticity is also prevalent in lab strains widely used to study *A. baumannii* biology. Successive subculturing of widely used strains and spontaneous genetic variations results in significantly altered genotypes and phenotypes, often not recognized by the scientific community. In addition, the current strain designation methods do not allow efficient communication about such differences. Even presumably identical strains from established culture collections have been found to demonstrate genetic heterogeneity. The "elephant in the (living) room" refers to the risk but also the potential of the bi-partite problem concerning the high diversity amongst *A. baumannii* isolates (inter-strain variability), and the universal issue of microevolution (intra-strain variability). This is generally ignored as it is not referenced adequately in scientific publications. We aim to raise awareness about the current issues and the problematic consequences generated by intra- and inter-strain diversity based on modern examples of *A. baumannii* isolates. Therefore, this review provides cases of broadly used *A. baumannii* strains and their genetic and phenotypic differences.

Acinetobacter baumannii and beyond

Acinetobacter baumannii is a Gram-negative opportunistic pathogen responsible for infections leading to considerable morbidity and mortality[1,2]. This bacterium belongs to the so-called ESKAPE group[3] that comprises multi-drug resistant (MDR) bacterial pathogens most often responsible for nosocomial infections. *A. baumannii* successfully thrives in hospital settings, including within intensive care units, and is not only resistant to many last-resort antibiotics but also disinfectants[4], human serum[5], phagocytosis by professional immune cells such as macrophages and neutrophils[6], and oxidative stress[7]. In addition, it can withstand prolonged periods of desiccation[4]. In this context, the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) designated carbapenem-resistant *A. baumannii* as a top priority for research and development of new antibiotics and as an urgent threat to public health[8,9]. The *A. baumannii* genome has a guanine-cytosine content of 39% and an average size of 3.9 Mb. It is highly dynamic and diverse, with zero to several plasmids; on average, 83.5% of the encoded genes are present only in a fraction of the previously investigated strains, generating an open pan-genome that currently has 51,000 unique genes[10,11]. This plasticity is caused by the presence of mobile genetic elements such as plasmids, insertion sequences, integrons, and bacteriophages, as well as *A. baumannii*'s potent capabilities for recombination and natural transformation[12–16].

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The inter-bacterial strain diversity (defined as the genomic heterogeneity amongst different *A. baumannii* isolates[17]) contrasts with the observation that most of our knowledge concerning *A. baumannii* biology, physiology, resistance, and virulence is derived from studies with a limited set of established strains, i.e., the historical, non-MDR strains ATCC17978 and ATCC19606^T, and the contemporary, MDR AB5075 strain. ATCC19606^T is the type strain of *A. baumannii* species, meaning the permanent prototypic strain to which all other strains must be compared to be included in the species according to conventional taxonomic criteria[18–20]. Conversely, ATCC17978 and AB5075 are reference strains widely used within the scientific community but without formal status in *A. baumannii* taxonomy[21]. Both type and reference strains can be obtained from various culture collections for comparative analysis. Furthermore, the rapid evolution of *A. baumannii* plastic genomes, generating intra-bacterial strain diversity (defined as genetic changes occurring within the same bacterial isolate), raises questions about whether these strains, obtained from culture collections or other repositories and shared and maintained in laboratories worldwide, still reflect their parental counterparts. We provide a non-exhaustive list of broadly used strains and some of their variants in Table 1. Furthermore, the major findings influencing phenotypic traits of *A. baumannii* AB5075, ATCC17978, and ATCC19606^T are summarized in Fig. 1.

Currently, whole-genome sequencing validation of strains is not systematically performed; hence, there is a risk of strain divergence at the genetic and phenotypic levels. Microevolution of bacterial strains is a known phenomenon that is not restricted to *A. baumannii*, as significant microevolution has been observed in bacteria such as *Escherichia coli*[22], *Pseudomonas aeruginosa*[23], *Vibrio cholerae*[24], *Legionella pneumophila*[25] and *Helicobacter pylori*[26]. However, systematic characterization of bacterial isolates used in scientific studies is generally not carried out or documented to identify the differences (genetic and phenotypic) among existing strain variants with the same name designation. Instead, even when identified, these non-systematically reported variations are informally shared between laboratories, but most often not reported in the resulting scientific studies. Therefore, the improved scientific communication proposed here will generally apply outside the *A. baumannii* field.

Here, we provide concrete examples from the *A. baumannii* field to illustrate a bi-partite cause of microorganism genetic diversity: (i) high genomic diversity amongst *A. baumannii* isolates from different origins (inter-strain diversity) and (ii) microevolution (intra-strain diversity). In addition, we discuss the phenomenon of phenotypic heterogeneity through phase variation. The implications go beyond the *A. baumannii* field, with different inter- and intra-strain diversity ratios depending on the genome dynamics and the lifestyle of the microorganisms considered.

Strain ATCC19606^T

A. baumannii ATCC19606^T is the type strain of *A. baumannii* species[27] and is available in many international culture collections with different designations. It was isolated from a human urine sample in the USA before 1949 and has since been one of this species' best-characterized strains[28]. Strain ATCC19606^T is a non-MDR strain susceptible to many antibiotics[29,30]. The chromosomal dihydropteroate synthase gene (*sul2*) confers resistance to sulphonamides, and a plasmid-borne *ohr* gene provides resistance to peroxides[29]. Strain ATCC19606^T was used to study sulphonamide resistance[31] and to characterize several virulence factors such as those involved in surface adherence[32,33], biofilm formation[34], iron uptake[35], immune evasion[36], quorum sensing[37], extracellular phospholipase[38], and mobile genetic elements such as IS*CR2*[39] and IS*Aba11*[40,41]. However, comparing different isolates from ATCC19606^T revealed considerable genetic differences, many likely of functional relevance[42]. The sequence variations ranged from SNPs to micro- or macro-deletions, and the presence or absence of a 52 kb prophage of the *Vieuvirus* genus[42] illustrates the degree of genome evolution. Intriguingly, the prophage designated Φ19606, carries the *eptA1* gene, encoding a functional lipid A phosphoethanolamine transferase, responsible for colistin resistance when induced by low calcium and magnesium levels[43]. Hence, the widely used strain ATCC19606^T has multiple genetically different variants, which may affect several important phenotypes.

Strain ATCC17978

A. baumannii ATCC17978 was isolated in 1951 from a 4-month-old infant with fatal meningitis[44,45]. Strain ATCC17978 is resistant to some β-lactams (it is sensitive to ticarcillin, cephalosporins, or carbapenems) and sulphonamides. ATCC17978 was first sequenced in 2007 using pyrosequencing[46]. Re-sequencing in 2015 using PacBio[47] revealed that the 148 kb conjugative plasmid pAB3 was incorrectly assembled into the chromosome[47]. Kröger et al.[48], performed RNA-seq analyses on strain ATCC17978 and noticed that pAB3 was lost during shipment between two laboratories. Hence, plasmid pAB3, which contains a molecular switch for the Type VI secretion system (T6SS), can be easily lost in a non-selective environment[47], rendering T6SS active. This suggests adaptation to an antibiotic-containing environment in which the acquisition of resistance via horizontal gene transfer can be beneficial[47]. Recently, a study by Wijers et al.[49], identified two variants of *A. baumannii* ATCC17978 that differ by a 44-kb accessory locus named AbaAL44 (*A. baumannii* accessory locus 44 kb). The authors analyzed deposited sequence data and found that published studies used both variants of the same parental strain of ATCC17978. Notably, the American Type Culture Collection (ATCC)-derived laboratory stocks comprise a mix of these two variants. These two variants differ at the genomic level and exhibit distinct phenotypic host-pathogen interactions in vitro and in vivo. AbaAL44 encodes putative virulence genes because the infections with the strain harboring AbaAL44 differ from the variant lacking AbaAL44 in the mouse pneumonia model[49]. Moreover, ATCC17978 is somehow unique regarding its iron uptake capability since it carries the rare fimsbactin siderophore gene cluster on the Tn*6552* mobile element that has been detected in < 1% of *A. baumannii* isolates[50]. These observations have alerted the community that widely used strains of *A. baumannii*, even when obtained from culture collections like ATCC, have and are likely still undergoing evolutionary changes and display genomic and phenotypic instability.

There are also examples of how specific mutations within *A. baumannii* strains have influenced the literature. In 2020, Powers and colleagues[51] reported that a single-nucleotide polymorphism (SNP) in an ATCC17978 strain variant had impacted a previous study[52] focused on the transport of membrane glycerophospholipids in Gram-negative bacteria. The SNP mapped to *obgE*, a gene encoding a GTPase involved in stringent response that revolves around producing GTP-derived nucleotide alarmones (p)ppGpp. Typically, nucleotide alarmones accumulate during nutritional stress and lead to significant changes in bacterial physiology that include the inhibition of de novo fatty acid biosynthesis[53]. Deleting genes required for lipid transport in ATCC17978 with the aberrant *obgE* allele resulted in a synthetic sick phenotype[51]. Along with other findings by Powers and colleagues[51], it was found that the *obgE* mutation invalidated previous results[52]. However, these studies were performed before detecting the AbaAL44 locus and other genetic differences in ATCC17978 by Wijers et al.[49]. In conclusion, there is clear evidence of genetic and phenotypic diversity in *A. baumannii* strain ATCC17978; however, the current strain designation does not reflect these significant differences, and scientific studies do not systematically report which of the two variants (or a mixture of both) is used, rendering any attempt to reproduce and even compare published observations challenging.

Strain AB5075

A. baumannii strain AB5075 was obtained in 2008 from a combatant wound infection[54]. It exhibits higher virulence in animal models than the historical strains ATCC19606^T and ATCC17978 and is regarded as a contemporary MDR *A. baumannii* strain[54]. AB5075 has three plasmids (p1AB5075, p2AB5075, and p3AB5075), with resistance island 2 on the largest plasmid p1AB5075, while resistance island 1 is localized on the chromosome[15]. Strain AB5075 is susceptible to tellurite, tetracycline, hygromycin, and apramycin, making it compatible with genetic

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Table 1 | A non-exhaustive list of broadly used *A. baumannii* strains and some of their variants including sequencing platform and assembly software, if available

GIVEN NAME	REFERENCE	GENBANK ACCESSION NUMBERS	SEQUENCING PLATFORM*	ASSEMBLER*
AB5075-UW	15,54	BioSample: SAMN36911450, JAVSCP000000000.1, SAMN02894434	MiSeq (Illumina), PacBio	Unicycler, HGAP v. 2.0
AB5075-VUB	56	BioSample: SAMN17898087, CP070362.2 (chromosome), CP070363.1 (pAB5075-VUB_1), CP070364.1 (pAB5075-VUB_2), CP070365.1 (pAB5075-VUB_3)	Oxford Nanopore MinION; Illumina	Flye v. 2.8.2
AB5075_WT	74	BioSample: SAMN10580593, SRA: SRS4138705	MiSeq (Illumina)	N/A
AB5075	75	BioSample: SAMN20368080, SRA: SRS9575594	MiSeq (Illumina)	N/A
AB5075-BLOKESCHLAB	76	BioSample: SAMN31681936, SRA: SRS15726398	PacBio RSII	HGAP v. 3.0
ATCC 17978	46	BioSample: SAMN02604331, CP000521.1 (chromosome), CP000522.1 (pAB1), CP000523.1 (ATCC 17978 pAB2)	454	Sequencher assembly program (Gene Codes)
17978-MFF	47	BioSample: SAMN03817043, CP012004.1 (chromosome), CP012005.1 (pAB3)	Illumina; PacBio	SPAdes v. 2.5.0; HGAP v. 2.2.0.133377-patch-3
17978 VU	49,77	BioSample: SAMN04273153, CP018664.1 (chromosome)	MiSeq (Illumina)	Geneious v. 9.1.5
17978 UN	49	BioSample: SAMN20326334, CP079931.1 (chromosome), CP079932.1 (pAB3), CP079933.1 (pAB1), CP079934.1 (pAB2)	Oxford Nanopore	Unicycler v. 0.4.8
ATCC17978-VUB	17	BioSample: SAMN25131675, CP091335.1 (chromosome)	Oxford Nanopore MinION; Illumina	Flye v. 2.9
ATCC17978-BLOKESCHLAB	76	BioSample: SAMN15507625, CP059041.1 (chromosome), CP059042.1 (plasmid unnamed)	PacBio RSII	HGAP v. 3.0
ATCC 17978	78	BioSample: SAMN14217790, CP049363.1 (chromosome), CP049364.1 (pAB1), CP049365.1 (pAB2)	PacBio	Pacbio v. 20 K
ATCC 17978 SUBSTR. LAB-WT	79	BioSample: SAMN11304548, CP039028.2 (chromosome), CP039027.1 (plasmid unnamed1), CP039029.1 (plasmid unnamed2), CP039030.1 (plasmid unnamed3)	PacBio	PacBio SMRT Analysis v. 2.3.0
ATCC17978	80	BioSample: SAMN35788762, SRA: SRS18007186	NovaSeq 6000 (Illumina)	N/A
ATCC17978 M_AB_NON_SELECTIVE	81	BioSample: SAMN37365860, SRA: SRS18868469	HiSeq X Ten (Illumina)	N/A
ATCC17978	Leyn A,S.; Sanford Burnham Prebys Medical Discovery Institute (Unpublished)	BioSample: SAMEA6463085, CACVBA000000000.1 (4 contigs)	Nanopore + Illumina	N/A
AB_ATCC17978	Monk,J.M.; UC San Diego (Unpublished)	BioSample: SAMN14779651, CP053098.1 (chromosome), CP053099.1 (plasmid unnamed1), CP053100.1 (plasmid unnamed2)	Oxford Nanopore MinION; HiSeq (Illumina)	Unicycler v. 0.4.2
ATCC17978	Third Military Medical University, China (Unpublished)	BioSample: SAMN06169813, SRA: SRS1874154	HiSeq 2500 (Illumina)	N/A
ATCC19606	82	BioSample: SAMD00206871, AP022836.1 (chromosome), AP022837.1 (pATCC19606-1), AP0228338.1 (pATCC19606-2)	Illumina MiniSeq; ONT MinION	Unicycler v. 0.4.6.
ATCC 19606	83	BioSample: SAMN12389466, CP045110.1 (chromosome), CP045108.1 (p1ATCC19606), CP045109.1 (p2ATCC19606)	Illumina MiSeq; Oxford Nanopore MinilON	"Hybrid assembly v. July-31"
ATCC19606-VUB	17	BioSample: SAMN25131676, CP091334.1 (chromosome)	MiSeq (Illumina)	Geneious v. 9.1.5
ATCC19606-BLOKESCHLAB	74	BioSample: SAMN15507635, CP059040.1 (chromosome)	PacBio RSII	HGAP v. 3.0
ATCC 19606	40	BioSample: SAMN13045090, CP046654.1 (chromosome), CP046655.1 (pMAC)	PacBio RSII	HGAP v. 3.0
ATCC19606	78	BioSample: SAMN35788763, SRA: SRS18007187	NovaSeq 6000 (Illumina)	N/A

N/A Not Available, *based on GenBank metada.

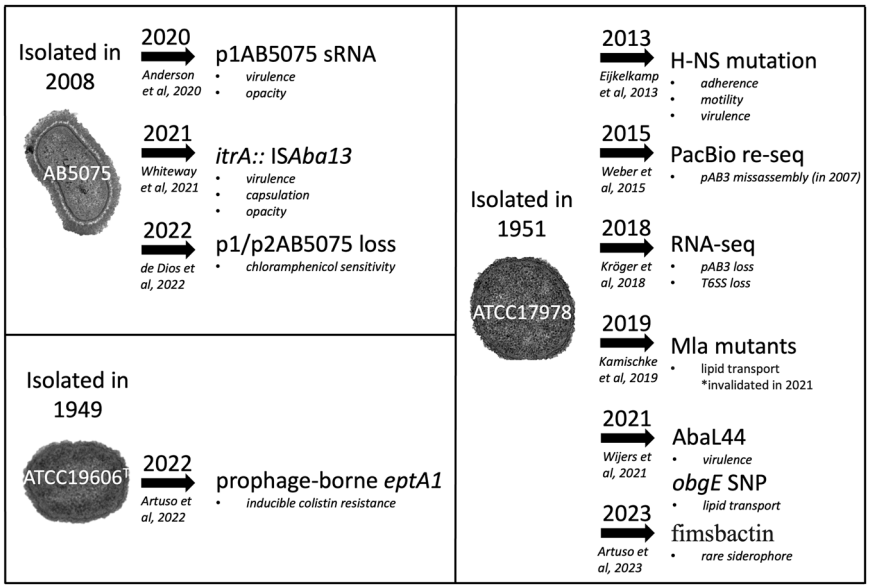

Fig. 1 | A graphical depiction of the most prominent variations in the phenotypic traits of *A. baumannii* AB5075, ATCC17978, and ATCC19606^T. The TEM micrographs were adapted from Valcek et al., 2023[17].

manipulation[54–56]. A saturated and ordered Tn*5* transposon library was successfully generated[15]. A recent study by Whiteway et al.[56] identified two circulating variants of AB5075 with distinct genotypes and phenotypes associated with capsule formation, an essential virulence factor[56]. The colonies of the AB5075 strain, obtained from two different laboratories, varied in opacity, mucoidy, and in vivo virulence due to the presence or absence of the polysaccharide capsule[56]. Mechanistic studies showed that capsule formation was modulated by the insertion/excision of the mobile genetic element IS*Aba13* in one of the genes (*itrA*) present in the locus for capsule synthesis. However, the frequency of this mutation in the laboratory strains remains to be explored. A further genetic variation within p1AB5075 was observed by Anderson et al.[57], who described a tandem amplification of an integron carried by p1AB5075, which regulates virulence, opacity, and global gene expression via levels of sRNA[57]. For example, while constructing a deletion mutant in the chloramphenicol resistance gene *craA*, de Dios et al.[55] isolated a spontaneously p1AB5075-curated Δ*craA* mutant, with the loss of the plasmid occurring during the mutagenesis procedure. This mutant strain showed a much higher chloramphenicol sensitivity than the wild-type strain and the single Δ*craA* mutant, which could be complemented by reintroducing the *craA* open reading frame. Interestingly, the loss of p1AB5075 alone did not increase sensitivity to chloramphenicol, thus complicating the association of the chloramphenicol resistance phenotype with the presence of this plasmid. Eventually, the genotype could only be assessed by PCR detection of the p1AB5075, p2AB5075, and p3AB5075 plasmids, indicating that mutant complementation can have limitations in specific cases. Both p2AB5075 and p3AB5075 plasmids were absent from a complete genome of AB5075 using long-read technology (PacBio) (GCF_028583505.1)[55]. However, this phenomenon is also known to be caused by the DNA library preparation and sequencing method[58]. In conclusion, as for *A. baumannii* ATCC17978 and ATCC19606^T, naturally occurring variants of AB5075 display genotypic and phenotypic traits that significantly differ from the parental AB5075 strain. Furthermore, the stochastic native plasmid loss, which can even happen during the course of mutagenesis or genome editing procedures, can potentially affect the traits under study.

Inter -and intra-bacterial strain diversity as a pragmatic resource

Heterogeneity amongst bacterial isolates can aid in novel discoveries. The outer leaflet of the outer membrane of Gram-negative organisms contains either lipopolysaccharide (LPS) or lipooligosaccharide (LOS). This unique glycolipid is essential for the growth of most Gram-negative bacteria[59]. However, some *A. baumannii* strains can become LOS-deficient in response to selection with cationic polymyxin antibiotics[60]. Polymyxins directly interact with negatively charged LPS/LOS, perturbing membrane structure and eventually killing the bacterial cell[61]. By comparing differences in multiple widely used strains such as ATCC17978, ATCC19606^T, and AB5075, it was shown that only strains with naturally low levels of penicillin-binding protein 1A (PBP1A), a class A penicillin-binding protein involved in peptidoglycan synthesis, were able to become LOS-deficient[62]. Strain ATCC17978 has high levels of PBP1A and cannot become LOS-deficient, whereas ATCC19606^T and AB5075 have low levels of PBP1A and LOS-deficient bacterial cells are easy to isolate in response to polymyxin. Follow-up studies showed that high levels of PBP1A inhibit elongasome function, which is critical for LOS-deficient *A. baumannii*[60]. In addition, spontaneous variants with plasmid rearrangements or losses can be an asset in genetic studies. For example, a serendipitously obtained p1AB5075-curated derivative of AB5075 was used for assessing how the copy number of the resistance island 2, harbored in this plasmid, alters the switching frequency between virulent and avirulent cells[57]. Moreover, the stochastic loss of large conjugative plasmids, a widespread trait of *A. baumannii* strains, resulted in the discovery of plasmid-encoded Type VI secretion regulators[47]. The role of mobile genetic elements in *A. baumannii* is substantial and reaches beyond antimicrobial resistance, as *A. baumannii* bacteria also harbor phage-like plasmids. Most phage-like plasmids share an asparagine tRNA gene serving as an insertion site for mobile elements into the chromosome[63]. Furthermore, carriage of some plasmids, such as pAB5 in *A. baumannii* UPAB1 improves survival of the strain in a murine catheter-associated urinary tract infection model, and decreases the virulence in a murine pneumonia model via regulation of chromosomally-encoded virulence factors and secretion systems[64]. This further proves that plasmids regulate phenotypes and switch between virulent and persistent strategies.

Additionally, commonly used strains exhibit significant differences in their gene expression profiles. For example, *adeB* expression varies substantially between ATCC17978 and ATCC19606^T, a finding confirmed in a recent study by Lucaßen et al.[65]. Therefore, researchers should carefully consider the choice of comparator strains, especially when studying efflux pump-related resistance mechanisms, such as those involved in tigecycline resistance, but not only these.

Moreover, transcriptional regulators like H-NS (histone-like nucleoid structuring protein) can also drive intra-strain phenotypic variation. In *A.*

baumannii ATCC17978, disruption of an *hns*-like gene resulted in a hypermotile phenotype, increased adherence to human pneumocytes, and heightened lethality in *Caenorhabditis elegans*[66]. These mutants also exhibited altered fatty acid composition and surface hydrophobicity, likely contributing to enhanced motility and host interaction. Transcriptome analysis revealed that disruption of the global repressor affected expression of virulence-associated loci, including the autotransporter Ata, a Type VI secretion system, and a Type I pilus cluster. These findings highlight how loss of H-NS-mediated repression can cause transcriptomic and phenotypic differences within a single strain[66].

In this context, the growing list of existing variants that diverged from a common parental strain represents, per se, a potential pragmatic resource that deserves to be exploited. One of the richness of *A. baumannii* resides in its intrinsic diversity, which can be used as a valuable resource rather than a pitfall. Because of the high genomic heterogeneity amongst *A. baumannii* bacterial isolates, the variants derived from a common parental strain can efficiently help generate important new mechanistic insights because of their high genomic similarity compared to less related bacterial isolates. This can only be achieved by systematically and accurately identifying the strain variants studied, traceable by a specific name and linked information. However, detailed information on the bacterial strain used in scientific studies is generally missing, perpetrating miscommunication worldwide[67]. That long-lasting issue can be turned into a helpful resource if correctly documented and shared amongst the scientific community. In essence, 'FAIR data' (Findable, Accessible, Interoperable, and Reusable) principles are especially key regarding bacterial strain microevolution. Working on the same strain makes data and resulting information interoperable and reusable. But only when the isolates are isogenic, which is not always the case. Identifying the differences and sharing this information in research papers is essential and may lead to unexpected discoveries. Modern initiatives exist. Setting up an open-access database and strain repository that brings together genomic data, phenotypic characterization, and the bacterial strains (parental and derived variants) will help the community, as recently proposed for the so-called "Acinetobase"[68]. The "Ab-web" is a dedicated website on *A. baumannii*, a workplace that can efficiently help communication[69].

A high-frequency switch generates phenotypic heterogeneity in *A. baumannii*

A. baumannii can rapidly interconvert between two cell subpopulations, distinguished by their opaque or translucent colony phenotypes when viewed by oblique lighting[70,71]. While this phenotypic heterogeneity has been observed in various clinical and environmental isolates, it has primarily been studied in AB5075. The switch between opaque and translucent variants occurs at frequencies of 10–20% in either direction and is regulated by cell density[71]. Multiple phenotypic differences exist between opaque and translucent variants. The opaque variant is significantly more motile, secretes the quorum sensing signal 3-OH C12-HSL, and has a capsule that is 2-fold thicker than the AV-T (avirulent-translucent) variant[70,71]. The AV-T variant forms more robust biofilms with a 2-fold greater cell mass and is better able to grow in nutrient-limited media. Most importantly, only the opaque variant is virulent in a mouse lung infection model and was recovered from the blood of patients with *A. baumannii* bacteremia[71]. Based on this, the virulent opaque variant was designated VIR-O, and the avirulent translucent variant AV-T. RNA sequencing analysis has shown that VIR-O and AV-T variants have 116 genes differentially expressed[71]. Interestingly, the avirulent AV-T variant exhibits increased expression of various transport systems and catabolic pathways for atypical carbon sources, which likely allows for the utilization of a wide variety of compounds as nutrients. Based on this information and the fact that the AV-T form is more adept at biofilm formation[70,71], it can be hypothesized that the AV-T variant is better suited for environmental survival outside the host.

The switch between VIR-O and AV-T states is mediated by the stochastic activation of at least four TetR-type transcriptional regulators (TTTRs); ABUW_1645, ABUW_1959, ABUW_2818 and ABUW_3353[72]. Individual expression of each TTTR is sufficient to drive VIR-O cells to the AV-T state, and each shares a common set of genes under their control, as well as uniquely regulated genes[72]. These TTTRs can be activated alone or in different combinations in VIR-O cells to mediate the switch to the AV-T state[72]. The combinatorial activation of the TTTRs creates another layer of phenotypic heterogeneity, as the resulting translucent variants all have unique phenotypes, including one translucent subvariant that remains virulent, while the majority of translucent subvariants are avirulent[72].

Moreover, a third variant, in addition to AV-T and VIR-O, was identified as a low-switching opaque (LSO) variant[57]. The LSO variant is regulated by tandem amplification of a p1AB5075 plasmid-borne integron, which modulates phenotypic switching and virulence via a putative ~300-nt sRNA encoded at the 5′ end of the *aadB* gene. LSO variants harbor fewer copies of this locus, show a ~ 3-log reduction in switching to AV-T, and exhibit attenuated virulence in murine lung infections. Transcriptional profiling revealed differential expression of over 100 genes, including several linked to virulence, suggesting a global regulatory role for the sRNA[57].

The ability to distinguish between VIR-O and AV-T subvariants is very difficult under room lighting on standard LB agar plates. For unclear reasons, the opacity differences between opaque and translucent variants are far more prominent on 0.5X LB agar plates, where both nutrients and agar concentration are lower. It is strongly advised that strains be routinely monitored for their opacity phenotype, as cultures can easily become mixed, especially if grown to high density. While many *A. baumannii* strains exhibit this switch, the only strain where we have been unable to detect switching is ATCC17978. Methods for distinguishing between the opaque and translucent variants have been described[73].

While in-strain switch-regulated heterogeneity has been described above, it is important to consider these phenomena happening in already heterogeneous species. This has already been demonstrated, as the clinical isolates exhibit tremendous heterogeneity in capsular polysaccharide production and compactness, virulence, and the macrocolony type to an already heterogeneous genome[17].

Conclusions

Recently published data showed the worldwide presence of distinct variants of three broadly used strains of *A. baumannii* (ATCC19606^T, ATCC17978, and AB5075). Variants of supposedly identical isolates could bring significant biases, leading to irreproducible, controversial, or even misleading results that may affect future studies. Yet, these variants illustrate the genomic and phenotypic complexity of *A. baumannii*, and awareness of such diversity has successfully led to significant discoveries. An increasing number of studies highlight the diversity within the "same" parental strain and the continuous evolutionary changes mainly fueled by genetic drift, horizontal gene transfer, and mobile genetic elements. The above-mentioned genetic differences amongst *A. baumannii* strains are likely to represent only the tip of an iceberg, and we predict that more undetected variants exist with an identical strain name. This phenomenon does not specifically impact the established strains described here, nor exclusively the ATCC strains, but most likely happens to a certain extent with any bacterial isolates sub-cultured and shared between laboratories.

Data availability

No datasets were generated or analysed during the current study.

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Author contributions

A.V. and C.V. drafted the manuscript. P.R., P.V., X.C., M.L., I.E., P.H., A.C., B.U., N.K., S.T., T.C., R.M., R.d.D., and C.K. implemented the review. All authors have read and approved the manuscript.

Competing interests

The authors declare no competing interests.

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