SUPPORTING INFORMATION

Evolving Carbapenemases: Can Medicinal Chemists Advance One Step Ahead of the Coming Storm?

(Perspective)

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Additional Information on the Epidemiology of Clinically Important Carbapenemases

1. OXA β-Lactamases

Today, OXA-23 has been isolated in other European countries (Ireland,[1] Belgium,[2] Bulgaria,[3] and Germany[4]), but also in Africa (Tunisia[5]), Asia (Turkey,[6] Iran,[7] United Arab Emirates,[8] China,[9] Singapore,[10] Thailand,[11] and Korea[12]), including Asian-Pacific Nations,[13, 14] South America (Brazil[15]), and North America (U.S.[16-18]).

Several of the 162 variants of OXA β-lactamases documented to date also possess the ability to inactivate carbapenems, including OXA-24, isolated in Spain,[19] Iran,[7] Asian-Pacific Nations,[13] the U.S.,[17, 18] and Italy,[20] OXA-40, isolated in Portugal,[21] the U.S.,[16] Spain[22] and Asian-Pacific Nations,[13] OXA-48, isolated in Turkey[23] and Belgium,[24] OXA-51, isolated in Argentina,[25] Iran,[7] and South Korea,[26] OXA-58, isolated in France,[27] Argentina,[28] Greece,[29] Singapore,[10] Italy,[30] China,[9] Spain,[31] Lebanon,[32] Taiwan,[33] Bulgaria,[3] Ireland (GenBank accession code ACI25602), Turkey,[6] South Korea,[34] and Asian-Pacific Nations,[13] OXA-66, isolated in China,[35] Taiwan,[36] Greece,[29] France,[37] and South Korea,[34] OXA-72, isolated in China,[9] Taiwan[38] and South Korea,[34] OXA-83, OXA-109, and OXA-115, isolated in South Korea[34] (OXA-109 also in the U.K.[39]). These represent a few examples to illustrate the diversity and ubiquity of OXA β-lactamases.

2. *Klebsiella pneumoniae* Carbapenemases (KPCs)

KPC-2 and KPC-3 were first isolated in the eastern U.S. and then spread to other states and countries. KPC-2 was first isolated in North Carolina in 1996,[40] then also in Maryland,[41] Massachusetts,[42] New York,[43-45] Pennsylvania,[46] Delaware, Ohio,[47] Arkansas, Vrginia,[48] Missouri,[49] and recently also in more southern (Texas,[50] Georgia,[51] Florida[52]) and western (Colorado, New Mexico, Arizona, and California[51]) states. It has also been isolated outside the U.S.: in Israel,[53] France,[54] Greece,[55] Norway,[56] China,[57] Colombia,[58] Brazil,[59] Ireland,[60] Canada,[61] and Trinidad & Tobago.[62] Figure 4 in the main text shows the geographical distribution of KPC enzymes. KPC-3 was first isolated in New York in 2000.[63] It differs from KPC-2 only by a H272Y mutation. In a kinetic study,[64] this enzyme seemed to be more efficient toward a broad range of antibiotics, especially cephalosporins and carbapenems, than KPC-2.[40, 43] It has to be noted, however, that the kinetic data were acquired in different laboratories and may not be directly comparable. Similar to KPC-2, this enzyme has subsequently been isolated in other areas of the U.S. (Pennsylvania and Ohio[65] and California[66]) and other countries (Israel,[67] the U.K.,[68] and Sweden[56]). KPC-4 and KPC-5 were both isolated in Puerto Rico.[69] Figure 5 in the main text shows the relationship between KPC enzymes visualized by a phylogenetic tree. KPC-5 seems to be an evolutionary intermediate between KPC-2 and KPC-4: KPC-5 deviates from KPC-2 by one mutation (P103R), while KPC-4 deviates from KPC-2 by two mutations (P103R and V239G). These two variants are less efficient carbapenemases than KPC-2, but they inactivate the cephalosporin ceftazidime (Figure 3 in the main text) more efficiently.[69] It is conceivable that these enzymes took the evolutionary pathway KPC-2 → KPC-5 → KPC-4 to better inactivate ceftazidime, but also the evolutionary pathway KPC-4 → KPC-5 → KPC-2 to better inactivate carbapenems is possible. KPC-4 has also been isolated in Scotland (GenBank accession code AAU06362). Several other KPC variants have been isolated

and their sequences deposited, but not published yet in the form of articles: KPC-6 in Puerto Rico in 2008 (GenBank accession code ACB71165), KPC-7 in the U.S. in 2008 (GenBank accession code ACE62798), KPC-8 in Puerto Rico in 2008 (GenBank accession code ACI95258), KPC-9 in Israel in 2009 (GenBank accession code ACM91559), and KPC-10 in Puerto Rico (GenBank accession code GQ140348).

3. IMP β-Lactamases

After being isolated first in Japan,[70, 71] IMP-1 was isolated in several other Asian countries (South Korea,[72] Singapore,[73] China[74], Taiwan,[75] Turkey,[76] and Lebanon[77]), in Europe (Italy,[78] the U.K.,[79] Spain,[80] and France[81]), and South America (Brazil[82]). The global spread of IMP-1 and other IMP variants is shown in Figure 6 of the main text.

IMP-2 was first isolated from *Acinetobacter baumannii* in Italy in 1997.[83] This enzyme was also isolated from *Serratia marcescens* in Japan (GenBank accession code AB182996). Its relatively low amino acid sequence identity (85%) to IMP-1, the difference between the gene cassettes carrying the IMP-1 and IMP-2 encoding genes, and the different geographic origins suggest different phylogenetic origins of IMP-1 and IMP-2.[83] The substrate spectrum of IMP-2 was overall similar to that of IMP-1 (penicillins, cephalosporins, and carbapenems, but not aztreonam), however, with significantly lower catalytic efficiencies toward ampicillin and cephaloridine and significantly higher catalytic efficiencies toward carbenicillin and meropenem[83] relative to IMP-1.[84] The phylogenetic tree in Figure 7 in the main text shows that IMP-1 and IMP-2 belong to two distinct groups of closely related enzymes; we will discuss these two groups in the following.

IMP-1 has four published homologs: IMP-6,[85] which differs by a S262G mutation; IMP-3,[86] which differs by a S262G mutation and a E126G mutation; IMP-10,[87] which differs by a V67F mutation; and IMP-26 (GenBank accession code EU541448), which differs by a G232S mutation and a S262G mutation from IMP-1. All of these enzymes of the "IMP-1 cluster" were isolated in Japan, the apparent origin country of IMP-1, or South Korea: IMP-6 from *Serratia marcescens*,[85] IMP-3 from *Shigella flexneri*,[86] IMP-10 from *Pseudomonas aeruginosa* and *Alcaligenes xylosoxidans*,[87] and IMP-26 from *Pseudomonas aeruginosa*. IMP-6 and IMP-3 have almost identical substrate spectra that deviate from that of IMP-1 in that catalytic efficiencies are smaller toward cephaloridine, ceftazidime, penicillins, and imipenem[88, 89] but higher toward meropenem.[85] This indicates that the mutation at position 126 has little impact while the one at position 262 has a significant, substrate-specific effect. Site-directed mutagenesis showed that alanine at this position confers catalytic efficiencies that are intermediate to those conferred by glycine (IMP-6) and serine (IMP-1) and that valine creates higher catalytic efficiencies toward nitrocefin, cephalothin, and cefotaxime, but very low catalytic efficiencies toward ceftazidime, penicillins, and imipenem.[89] It seems that IMP-1 may have evolved from IMP-3 via IMP-6 to acquire a broader substrate spectrum, while the intermediate, IMP-6, has an evolutionary advantage over IMP-1 with respect to the inactivation of meropenem.[85] In agreement with this scenario, we did not find any reports on IMP-3 besides the original publication,[85] but IMP-6 has recently been found in clinical isolates of *Pseudomonas aeruginosa* in Japan (GenBank accession code AB188812) and South Korea.[90] IMP-10 exhibits slightly higher catalytic efficiencies toward most cephalosporins, but significantly lower catalytic efficiencies toward

most penicillins than IMP-1,[87] suggesting that it is a variant specializing in the inactivation of cephalosporins and carbapenems. IMP-10 was isolated on other occasions in Japan from *Pseudomonas aeruginosa*[91] and *Serratia marcescens*.[92] The addition of a longer bulky group in phenylalanine compared to valine at position 67 in the substrate binding site could be responsible for the decreased inactivation of penicillins.

IMP-2, IMP-8, IMP-19, IMP-20, and IMP-24 form another cluster of closely related enzymes, the "IMP-2 cluster". There are very few reports on IMP-2, indicating that it may be clinically less important than IMP-1, but several of its close variants have been reported repeatedly. IMP-19 differs from IMP-2 only by an R38A mutation and has been isolated from *Aeromonas caviae*, also in France like IMP-2. Its activity profile was quite different from that of IMP-2;[83] especially the catalytic efficiencies toward imipenem and meropenem were significantly lower,[93] suggesting that IMP-19 might be a precursor of IMP-2. However, it is not clear how comparable the data acquired in different laboratories are. Even though not published as articles, IMP-19 has also been found in *Achromobacter xylosoxidans*, *Enterobacter cloacae*, and *Pseudomonas putida* (GenBank accession codes AB201263, AB201264, and AB201265, respectively), *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (GenBank accession codes 184976 and 184977), supporting the possibility that IMP-2 might be a precursor of IMP-19. Residue 38 is very close to the N-terminus of the mature protein, which lies on top of the β hairpin loop covering the active site (PDB entry 1DD6[94]); thus, it could play a role in substrate binding. IMP-20, isolated from *Pseudomonas aeruginosa* in Japan (GenBank accession code AB196988), harbors an additional V67F mutation relative to IMP-19. Interestingly, IMP-20 has this mutation in common with IMP-10 relative to IMP-1. It would be interesting to see whether the changes in substrate profile between IMP-19 and IMP-20 parallel those between IMP-10 and IMP-1.[87] IMP-8 differs from IMP-19 by a V254G mutation. It has been isolated from *Klebsiella pneumoniae*[95] and *Enterobacter cloacae*[96] in Taiwan and from *Acinetobacter baumannii* in China.[97] IMP-24, isolated from *Serratia marcescens* in Taiwan (GenBank accession code EF192154), differs from IMP-8 by a K315R mutation. Since both mutations V254G (observed in IMP-8 and IMP-24) and K315R (observed in IMP-24) occur on the surface of the protein opposite the active site and are quite conservative, we do not expect them to have dramatic effects on catalytic efficiencies.

Two other pairs of IMPs, IMP-11 and IMP-21, as well as IMP-9 and IMP-25, differ only by one mutation. IMP-21 harbors a V67A mutation relative to IMP-11. We have observed the V67F mutation in IMP-10 where it was reported to decrease activity toward penicillins and in IMP-20, but the mutation to the short hydrophobic side chain in alanine is not expected to significantly affect the substrate spectrum. Both enzymes have not yet been characterized biochemically. IMP-11 has been isolated from *Acinetobacter baumannnii* and *Pseudomonas aeruginosa* in Japan (GenBank accession codes AB074436 and AB074437); IMP-21 was isolated from *Pseudomonas aeruginosa* in Japan (GenBank accession code AB204557). Overall, IMP-11 and IMP-21 deviate significantly from both the IMP-1 and IMP-2 clusters, but are a little closer to the IMP-2 cluster. IMP-25 (GenBank accession code EU352796) differs by a S262G mutation from IMP-9[98] (just like IMP-6 from IMP-1). Accordingly, we would hypothesize that IMP-9 has higher catalytic efficiencies toward penicillins, ceftazidime, cephaloridine, and imipenem than IMP-25. Both enzymes were isolated from *Pseudomonas aeruginosa* in China.

Overall these enzymes are also distant from the IMP-1 and IMP-2 clusters, but a little closer to the IMP-1 cluster.

The other published IMPs have not currently been found in clusters with very closely related variants. IMP-4 was first isolated in the late nineties from *Acinetobacter baumannii* in Hong Kong[99] and shortly after from *Citrobacter youngae* in China.[100] It is phylogenetically close to the IMP-1 cluster. In 2004, it was isolated from a patient with a *Pseudomonas aeruginosa* infection in Melbourne, Australia.[101] The IMP-4 gene was soon detected in several isolates of a clinical outbreak in Melbourne, including *Serratia marcescens*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Enterobacter cloacae,*[102] and subsequently also in *Acinetobacter junii*.[103] IMP-4 was also isolated from *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Citrobacter amalonaticus* in Sydney, Australia.[104] Later, it was also isolated from *Pseudomonas aeruginosa* in a French patient repatriated from Malaysia,[105] from *Acinetobacter baumannii* in Singapore,[10] from *Klebsiella pneumoniae* in China,[106] from *Acinetobacter johnsonii* on the Phillipines,[13] and from *Acinetobacter* spp. in Malaysia.[107] IMP-5 was isolated in 1998 from *Acinetobacter baumannii*[108] and later from *Pseudomonas aeruginosa*[109] in Portugal. This enzyme is more closely related to the IMP-1 cluster than to the IMP-2 cluster. The first IMP enzyme to be discovered in the Americas was IMP-7, which was isolated from *Pseudomonas aeruginosa* in Canada in 1995 and 1996.[110] IMP-7 is most closely related to IMP-5. It was later also isolated in Malaysia,[111] Slovakia,[112] Japan,[113] and the Czech Republic.[114] IMP-12 was isolated from *Pseudomonas putida* in Italy and is phylogenetically more closely related to the IMP-2 cluster than the IMP-1 cluster.[115] IMP-12 is mostly characterized by low catalytic efficiencies toward some penicillins relative to IMP-1.[115] IMP-13 was isolated from *Pseudomonas aeruginosa* in 2001 in Rome, Italy,[116] and in 2003 in a clinical outbreak of the same organism in southern Italy.[117] This enzyme is also closely related to the IMP-2 cluster. It has also been found in *Salmonella enterica* in Colombia,[118] in *Pseudomonas aeruginosa* in Romania,[119] Argentina,[120] and Austria.[121] IMP-14 and IMP-15 were both first isolated from *Pseudomonas aeruginosa* in Thailand (GenBank accession codes AY553332 and AY553333). Interestingly, these variants are not closely related. While IMP-14 is more closely related to the IMP-2 cluster, IMP-15 is more closely related to the IMP-1 cluster. IMP-15 was recently isolated from *Pseudomonas aeruginosa* in Kentucky, USA, and it was likely imported from Mexico, where the patient was injured and initially treated.[122] In fact, the enzyme was isolated from the same organism in Mexico in Guadalajara[123] and Mexico City.[124] IMP-16 was isolated from *Pseudomonas aeruginosa* in Brazil.[125] It is closely related to the couple IMP-11/IMP-21 and a little less closely to IMP-12. No catalytic efficiencies are available for IMP-11 and IMP-21, but the catalytic efficiencies of IMP-16[125] are remarkably similar to those of IMP-12,[115] especially with respect to low catalytic efficiencies toward penicillins and imipenem. IMP-17 has been assigned, but not published, yet.[126] IMP-18 was isolated from *Pseudomonas aeruginosa* in the U.S.,[127] Mexico,[128] and Puerto Rico.[129] IMP-18 is most closely related to IMP-14. IMP-22 was isolated both from *Pseudomonas fluorescens* in waste water and *Pseudomonas aeruginosa* in a teaching hospital in Italy[130] and in Austria.[121] While this enzyme is phylogenetically most closely related to IMP-16, its activity profile is more similar to that of IMP-1.[130] IMP-23 has been assigned but not yet published.[126]

4. VIM β-Lactamases

Apart from *Psdueomonas aeruginosa* in Italy, VIM-1 has been reported in other European countries (Greece,[131] Spain,[132] France,[133] and Germany[134]) and in Turkey,[135] but to our knowledge not outside these countries. In addition to *Pseudomonas aeruginosa*, this enzyme has also been isolated from *Klebsiella pneumoniae* and *Escherichia coli*,[132] *Enterobacter cloacae*,[136] *Acinetobacter baumannii,*[137] *Citrobacter freundii*,[134] *Klebsiella oxytoca*,[138] *Providencia stuartii,*[139] and *Serratia liquefaciens.*[140] The global spread of VIM-1 and other VIM enzymes is depicted in Figure 8 in the main text.

Twenty two variants of VIM-1 have been reported to date.[126] Their phylogenetic relationships are shown in Figure 9 in the main text. VIM-2, the second VIM enzyme to be reported, was actually isolated prior to VIM-1 in 1996 in France, also from *Pseudomonas aeruginosa.*[141] Its amino acid sequence is 90% identical to that of VIM-1 and it also hydrolyzes all tested β-lactam antibiotics except the monobactam aztreonam.[141] Its activity toward cephalosporins is similar to and that toward penicillins and carbapenems higher than that of VIM-1.[142] Geographically, VIM-2 is more widely spread than VIM-1. Besides France, it has been found in other European countries (Greece,[143] Portugal,[144] Poland,[145] Croatia,[146] Italy,[147] Germany,[148] Spain,[149] Belgium,[150] Hungary,[151] Romania,[119] the U.K.[152], Serbia,[153] and Austria[121]), but also in Asia (Korea,[154] Taiwan,[96] Japan,[155] Saudi Arabia,[156] China,[157] India and Russia,[158] and Turkey[159]), South America (Chile,[160] Venezuela and Brazil,[161] and Colombia[162]), North America (U.S.,[163, 164] Canada,[165] and Mexico[166]), and Africa (Tunisia[167] and Kenya[168]). Similar to VIM-1, VIM-2 has been isolated from several different species: originally *Pseudomonas aeruginosa*,[141] but then also from *Serratia marcescens*,[169] *Acinetobacter baumannii*,[170] *Citrobacter freundii*,[96] *Enterobacter cloacae*,[171] *Klebsiella oxytoca*,[172] *Klebsiella pneumoniae*,[173] *Achromobacter xylosoxidans*,[174] *Pseudomonas putida*,[175] *Providencia* spp.,[176] and *Enterobacter aerogenes*.[81] VIM-2 is also the only enzyme of the VIM group that has been crystallized, in complex with a mercaptocarboxylate inhibitor[177] and as the free enzyme both with an oxidized and reduced Cys221.[178]

VIM-3 is a variant of VIM-2 that was isolated from *Pseudomonas aeruginosa* in Taiwan.[179] This variant deviates from VIM-2 by only two mutations: Q59K (in the original publication falsely reported as G59K[179]) and N165S. In susceptibility assays, VIM-3 appeared to confer slightly higher resistance levels, especially toward ceftazidime, than VIM-2.[179, 180] To our knowledge, VIM-3 has not been reported outside Taiwan. VIM-4 differs from VIM-1 by only one mutation, S228R, and, just like VIM-1, has been isolated in Greece.[181] Arginine is also found at position 228 in VIM-2 and VIM-3. VIM-4 was subsequently isolated in other European countries (Sweden,[182] Italy,[183] Poland,[184] Hungary,[185] France,[186] and Belgium[187]), but also in North African Tunisia[188] and Australia.[189] Interestingly, VIM-4 isolated in Australia from a patient with a *Pseudomonas aeruginosa* infection was most likely transferred from Greece, where the patient was treated before being transferred to Australia. In addition, the patient was infected with *Acinetobacter baumannii* carrying OXA-58.[189] VIM-4 was isolated from *Pseudomonas aeruginosa*,[181] *Klebsiella pneumoniae* and *Enterobacter cloacae*,[183] *Acinetobacter* spp.,[186] *Pseudomonas putida*,[187] and *Aeromonas hydrophila*.[190] VIM-5 differs from VIM-4 by only four mutations: A130K, H224L, E225A, and K291T. This variant was isolated from *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* in Turkey in 2003.[191] Later on, it was

isolated in the same country from *Enterobacter cloacae*[192] and *Pseudomonas putida*,[193] and from *Pseudomonas aeruginosa* in India.[194] VIM-6 is most closely related to VIM-3, from which it differs by only one mutation, K59R. It was isolated from *Pseudomonas putida* in Singapore in 2000[195] and from *Pseudomonas aeruginosa* in India in 2006.[194] As the other VIM enzymes, VIM-6 is also integron-borne and efficiently inactivates all tested β-lactams except aztreonam.[196] VIM-7 is the first VIM enzyme to be isolated in the U.S.. Its gene was found on an integron in a *Pseudomonas aeruginosa* isolate in 2001.[197] VIM-2 was not isolated in the U.S. until 2003.[163] VIM-7 has less sequence identity (77%) to VIM-1 than any of the other variants up to VIM-6 (89 to 99%). It has therefore been suggested that VIM-7 has arisen independently in the U.S. rather than having been imported from Europe or Asia, where VIM-1 to VIM-6 have been reported first.[197] VIM-2, on the other hand, may have been disseminated to the U.S. from Jordan.[164] VIM-7 effectively hydrolyzes all tested β-lactam antibiotics except aztreonam.[142] Its activity toward cephalosporins is lower and that toward penicillins higher than that of VIM-2.[142] Its activity toward the two carbapenems imipenem and meropenem is similar to, but that toward ertapenem significantly higher than that of VIM-2.[142] It has been suggested that some of the changes in catalytic efficiencies may be due to a Y218F mutation.[142] VIM-8 is a VIM-2 variant that differs from that enzyme by only a T142A mutation. VIM-8 was isolated from *Pseudomonas aeruginosa* in Colombia.[198] Since VIM-2 has been found in this country as well,[199] VIM-8 may have evolved from VIM-2 or vice versa. No kinetic data have been reported for VIM-8, but the fact that it has been found in clinical isolates suggests that the T142A mutation has no significantly detrimental effect on enzyme activity. In crystal structures of VIM-2, T142 is at distances of about 10 Å from the active site Zn1 and 13 Å from Zn2.[177, 178] VIM-9 is also a point mutant of VIM-2 (and VIM-8) with a T142I mutation at the same position. This variant has been isolated from *Pseudomonas aeruginosa* in the U.K. (GenBank accession code AY524988), where VIM-2 has also been found.[152] The fact that threonine (VIM-2) can be mutated to either alanine (VIM-8) or isoleucine (VIM-9) by a single nucleotide change, but that two nucleotide changes are necessary to interconvert alanine and isoleucine suggests that VIM-2 is the common ancestor of VIM-8 and VIM-9 (see Figure 9 in the main text). VIM-10 was also isolated from *Pseudomonas aeruginosa* in the U.K. and is yet another point mutant of VIM-2, carrying a F258Y mutation.[200] VIM-11 was isolated from *Pseudomonas aeruginosa* in Argentina.[201] Interestingly, this enzyme seems to be an evolutionary intermediate between VIM-2 and VIM-3 or VIM-6: VIM-11 can be obtained from VIM-2 through a N165S mutation, and VIM-3 and VIM-6 can be obtained from VIM-11 through a Q59K and Q59R mutation, respectively.[201] VIM-11 was later also isolated from *Acinetobacter baumannii* in Taiwan[202] and from *Pseudomonas aeruginosa* in India.[194] Determination of kinetic constants of VIM-11 relative to VIM-2 revealed that VIM-11 exhibits higher catalytic efficiencies toward ceftazidime (four-fold), cefepime (three-fold), and cefpirome (two-fold).[203] VIM-12, isolated in Greece from *Klebsiella pneumoniae*, seems to be a hybrid of VIM-1 and VIM-2 with the N-terminal region corresponding to VIM-1 and the C-terminal region corresponding to VIM-2[204] (hence its position between the clusters around VIM-1 and VIM-2 in Figure 9 in the main text). It was suggested that VIM-12 may have arisen in a hospital environment, in which both VIM-1 and VIM-2 producing organisms are endemic.[204] This enzyme was later also isolated from *Escherichia coli*, also in Greece.[205] Biochemical characterization of VIM-12 revealed a narrow substrate spectrum,

limited to penicillins.[206] VIM-13 is a variant of VIM-1, exhibiting 93% sequence identity and was isolated from *Pseudomonas aeruginosa* on the Spanish Island Mallorca.[207] Its catalytic efficiency toward most tested β-lactam antibiotics was about double of that of VIM-1 except for ceftazidime and cefepime, for which its catalytic efficiency was lower.[207] VIM-14 was isolated from *Pseudomonas aeruginosa* in Italy (GenBank accession code AY635904) and Spain (GenBank accession code ABK63186) and differs from VIM-4 by only one mutation. VIM-15 and VIM-16 were isolated from *Pseudomonas aeruginosa* in Bulgaria and Germany, respectively.[208] They differ from VIM-2 by one mutation each: VIM-15 by Y218F, which was also observed in VIM-7, and VIM-16 by S54L, not observed in any other VIM variants.[208] Overall, VIM-15 exhibited higher catalytic efficiency toward all tested substrates than VIM-2 and VIM-16, and it was concluded that the Y218F mutation enhances catalytic efficiency, whereas S54L had no significant effect.[208] VIM-17 was isolated from *Pseudomonas aeruginosa* in Greece[209] and differs from VIM-2 only by a mutation in the leader sequence, that is, the mature protein is identical. VIM-18 was recently reported in *Pseudomonas aeruginosa* isolates in India.[194] This enzyme has a four-amino acid deletion compared to the other VIM enzymes.[194] VIM-19 has been isolated from *Providencia stuartii*, *Escherichia coli*, and *Klebsiella pneumoniae* isolates recovered from Algerian patients.[210, 211] It has two mutations, N215K and S228R, compared to VIM-1, and only one, S228R, compared to VIM-4. This variant hydrolyzes carbapenems better than VIM-1 and both mutations are critical for this improvement.[211] VIM-20 through VIM-22 have been assigned, but not published, yet.[126] VIM-23 was isolated from *Enterobacter cloacae* in Mexico (GenBank accession code GQ242167).

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