NDM carbapenemases in the United Kingdom: an analysis of the first 250 cases

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Objectives: Gram-negative bacteria with diverse carbapenemases, including New Delhi metallo-β-lactamase (NDM) enzymes, have been increasingly recorded in the UK since 2007. We analysed patient data for NDM-positive isolates confirmed by the national reference laboratory from UK laboratories from February 2008 to July 2013.

Methods: Isolates resistant to carbapenems and with imipenem MICs reduced ≥8-fold by EDTA were tested by PCR for genes encoding acquired class B carbapenemases. MICs were determined by BSAC agar dilution methodology. When requested by the sender, or when they were members of apparent clusters, NDM-positive isolates were typed by variable number tandem repeat (VNTR) analysis or PFGE. Data provided by the sending laboratories were collated and reviewed.

Results: From February 2008 to July 2013 the reference laboratory confirmed 326 NDM-positive isolates from 250 patients, submitted by 83 laboratories. Most (85%, 213/250) patients were already hospitalized when the NDM-positive bacteria were detected, were male (61%, 152/250) and were aged ≥60 years (58%, 145/250). Travel history was available for only 40% of patients, but 52% (53/101) of these had documented healthcare contact within or travel to the Indian subcontinent. Most NDM-positive isolates (94%, 306/326) were Enterobacteriaceae with just 6% (20/326) non-fermenters; the predominant hosts were Klebsiella spp. (55%, 180/326) and Escherichia coli (25%, 80/326). Almost all NDM-positive isolates were resistant to multiple antibiotic classes, but 90% remained susceptible to colistin.

Conclusions: Gram-negative bacteria with NDM carbapenemases are a growing challenge, especially for elderly hospitalized patients, including those with healthcare contact in the Indian subcontinent, and leave few therapeutic options. UK outbreaks remain rare and contained.

Keywords: MBLs, meropenem, Enterobacteriaceae, Pseudomonas, Acinetobacter

Introduction

Increasing antimicrobial resistance has recently been highlighted both nationally in the Chief Medical Officer for England’s annual report1 and internationally.2,3 Gram-negative bacteria carrying carbapenem-inactivating β-lactamases (carbapenemases) are an especial concern given that, until recently, carbapenems were the ‘reserve’ antibiotics for infections caused by bacteria already resistant to other agents. Acquired carbapenemases are produced by increasing numbers of Enterobacteriaceae (mostly Klebsiella spp.) and non-fermenters. They include metallo- (e.g. IMP, NDM, VIM) and non-metallo- (e.g. KPC, OXA-48) β-lactamases. New Delhi metallo-β-lactamases (NDMs) were first reported in 20094 and subsequently have been increasingly reported from across the world, often, though not always, in bacteria from patients with epidemiological links (healthcare contact and/or travel) to the Indian subcontinent or the Balkans region.5–8 Metallo-β-lactamases (MBLs), including NDM enzymes, are inhibited by metal ion chelators such as EDTA. They hydrolyse and confer resistance to carbapenems and other β-lactam antibiotics, except aztreonam.9 NDM-producing bacteria are also often resistant to fluoroquinolones, aminoglycosides and, owing to production of extended-spectrum β-lactamases (ESBLs) or AmpC enzymes, also to aztreonam.10 Therapeutic options consequently are extremely limited, with isolates often susceptible only to colistin, and more variably, tigecycline, fosfomycin and nitrofurantoin.10,11

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Since the first reports of NDM-type enzymes,\textsuperscript{4,10} the UK has seen more affected patients than most other countries in Western Europe.\textsuperscript{6} Here we review the first 250 UK cases recognized as infected or colonized by bacteria producing NDM-type enzymes, as ascertained by the Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit of Public Health England (PHE).

### Materials and methods

#### Bacterial isolates, identification and susceptibility testing

Isolates had been submitted to PHE's national reference laboratory, AMRHAI, from laboratories across the UK between February 2008 and July 2013 for investigation of resistance that was considered 'unusual' by the referring laboratories, including resistance to carbapenems. Bacterial identification was confirmed in AMRHAI using chromogenic agars [CHROMagar\textsuperscript{TM} Orientation (CHROMagar, Paris, France) and Brilliance UTI (Oxoid, Basingstoke, UK)], API-20E tests (bioMerieux SA, Marcy-l'Etoile, France) or, since August 2012, by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-ToF MS; Bruker Microflex LT, Bruker Daltonik GmbH, Bremen, Germany). In addition, in-house algorithms were used where required to identify unusual organisms by housekeeping gene sequence cluster analysis.

Antibiotic susceptibilities (MICs) were determined by BSAC agar dilution\textsuperscript{12} using AMRHAI's standard Gram-negative antibiotic panel, which included ertapenem, imipenem (tested with/without EDTA at 320 mg/L to detect likely MBL producers) and meropenem. MICs were interpreted using BSAC breakpoints, where available.\textsuperscript{13}

#### Screening for metallo-carbapenemase genes

Isolates resistant to one or more carbapenems and exhibiting a significant ($\geq$8-fold) reduction in imipenem MIC in the presence of EDTA were tested

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**Table 1.** Source and species for the NDM-positive isolates from different settings

<table>
<thead>
<tr>
<th>Species</th>
<th>Hospital setting</th>
<th>Unknown setting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>urines</td>
<td>clinical or screening swabs</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>64</td>
<td>47</td>
</tr>
<tr>
<td>E. coli</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Providencia spp.</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Morganella spp.</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serratia spp.</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>105</td>
<td>88</td>
</tr>
</tbody>
</table>

|                  | urines | clinical or screening swabs | blood cultures and line tips | respiratory | tissue and fluid | faeces | not known |
| Klebsiella spp.  | 3      | 1               | 0                | 0           | 0             | 0     | 1         |
| E. coli          | 1      | 0               | 0                | 0           | 0             | 0     | 0         |
| Serratia spp.    | 1      | 0               | 0                | 0           | 0             | 0     | 0         |
| **Total**        | 5      | 1               | 0                | 0           | 0             | 0     | 1         |

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GP, general practice.
Data are numbers of isolates.
by in-house PCR assays for genes encoding acquired class B (IMP, VIM, NDM, GIM, SIM and SPM) carbapenemases as previously described,\(^{14,15}\) and/or with a commercial microarray (Check-MDR CT102; Check-Points, Wageningen, The Netherlands).\(^{16}\)

### Typing

Where requested by the sending laboratories, isolates of Klebsiella pneumoniae were typed by variable number tandem repeat (VNTR) analysis of nine loci (A, E, H, J, K, D\(^{17}\) and N1, N2 and N4).\(^{18}\) Sequence types (STs) of representatives of the most frequently found VNTR types were determined by multilocus sequence typing (MLST).\(^{19}\) Pseudomonas aeruginosa isolates were typed by VNTR analysis of nine loci, as described previously\(^{20}\) and STs were determined using the scheme of Curran et al.\(^{21}\)

For other species, typing was carried out by PFGE of XbaI-digested (Escherichia coli, Enterobacter spp., Citrobacter spp.) or ApaI-digested (Acinetobacter spp.) genomic DNA, as described previously;\(^{17}\) pre-2010 isolates of K. pneumoniae were also typed by this method. VNTR profiles or gel images were analysed and compared using BioNumerics (Applied Maths, Sint-Martens-Latem, Belgium) software, version 6.1. Isolates sharing highly similar banding patterns (with a similarity of \(\geq 86\%\)) by PFGE were described as clusters, irrespective of whether or not there were epidemiological links between the source patients. MLST of E. coli cluster 1 was carried out as described by Wirth et al.\(^{22}\)

### Results

#### Demographics of patients affected and distribution

During the study period, AMRHAI confirmed 326 NDM-positive isolates, submitted by 83 UK laboratories from 250 patients. The isolates from 2008 were identified retrospectively after the initial characterization of the \(\text{bla}_{\text{NDM}}\) gene and later isolates were

<table>
<thead>
<tr>
<th>Antibiotic (range tested, mg/L)</th>
<th>BSAC breakpoint(s)(^{13})</th>
<th>Isolates</th>
<th>Number of isolates with MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\leq S/\geq R)</td>
<td></td>
<td>(&lt;0.125) 0.25 0.5 1 2 4 8 16 32 64 (\geq 128) NA % S</td>
</tr>
<tr>
<td>Ertapenem (0.125 – 16)</td>
<td>Enterobacteriaceae non-fermenters</td>
<td>(\leq 0.5/\geq 1) NT</td>
<td>1 1 2 10 290*</td>
</tr>
<tr>
<td>Imipenem (0.06 – 128)</td>
<td>Enterobacteriaceae non-fermenters</td>
<td>(\leq 2/\geq 8)</td>
<td>3 5 22 64 118 66 27 1 1</td>
</tr>
<tr>
<td>Meropenem (0.06 – 32)</td>
<td>Enterobacteriaceae non-fermenters</td>
<td>(\leq 8/\geq 16)</td>
<td>1 5 9 35 92 164*</td>
</tr>
<tr>
<td>Amikacin (0.5 – 64)</td>
<td>Enterobacteriaceae non-fermenters</td>
<td>(\leq 8/\geq 16)</td>
<td>1 1 19 17 19 10 15 6 1 218</td>
</tr>
<tr>
<td>Gentamicin (0.125 – 32)</td>
<td>Enterobacteriaceae non-fermenters</td>
<td>(\leq 4/\geq 4)</td>
<td>1 1 1 1 1 1 1 1 1 12</td>
</tr>
<tr>
<td>Tobramycin (0.125 – 32)</td>
<td>Enterobacteriaceae non-fermenters</td>
<td>(\leq 4/\geq 4)</td>
<td>1 10 8 3 2 9 19 17 238*</td>
</tr>
<tr>
<td>Ciprofloxacin (0.125 – 8)</td>
<td>Enterobacteriaceae non-fermenters</td>
<td>(\leq 0.5/\geq 1)</td>
<td>18 14 5 4 8 7 7 243*</td>
</tr>
<tr>
<td>Colistin (0.5 – 32)</td>
<td>Enterobacteriaceae non-fermenters</td>
<td>(\leq 2/\geq 2)</td>
<td>171° 98 7 1 1 7 4 3 7c</td>
</tr>
<tr>
<td>Tigecycline (0.25 – 16)</td>
<td>Enterobacteriaceae non-fermenters</td>
<td>(\leq 1/\geq 0.5)</td>
<td>49° 74 61 68 34 10 3</td>
</tr>
</tbody>
</table>

S, susceptible; R, resistant; NA, not available; NT, not tested; Ac, Acinetobacter spp.; Ps, Pseudomonas spp.

1. Cells highlighted in dark grey are resistant isolates; those in light grey are intermediate; and white are susceptible.
3. *P. aeruginosa and 16 Acinetobacter spp.
4. MIC greater than or equal to the value shown.
5. EUCAST breakpoint.
6. MIC less than or equal to indicated value.
7. Non-species-related breakpoint.
NDM carbapenemases in the UK

identified within 1–2 weeks of submission. The first known UK isolate with NDM carbapenemase in 2008 was an E. coli isolate from a rectal swab specimen taken from a 26-year-old hospitalized female patient who had a history of travel to India. The number of new patients affected (i.e. infected or colonized) increased year-on-year: 7 in 2008, 29 in 2009, 31 in 2010, 46 in 2011, 74 in 2012 and 63 in the first 7 months of 2013.

The regional distribution of affected patients from February 2008 to July 2013 was as follows: England (n=233), Scotland (n=7), Wales (n=4) and Northern Ireland (n=6); no region was spared. The largest number of patients was from London (n=88), followed by the West Midlands (n=39), Greater Manchester (n=23) and Yorkshire and Humber (n=21). Figure 1 shows the numbers of referring laboratories and patients per quarter during the study period and the proportions of new and known patients with NDM-positive bacteria, illustrating the ongoing rise in these numbers.

The majority (82%, 205/250) of the source patients were hospitalized, but 12% (30/250) were from primary care, 3% (8/250) had isolates taken from both these settings and the setting for hospitalization, but 12% (30/250) were from primary care, 3% (8/250) of patients was unavailable. Most isolates (58%, 152/250) were from male patients were >60 years of age. Patients in primary care were likewise mainly male (58%, 22/38), and 86% (19/22) of these male patients were >60 years of age.

Rudimentary travel history was available for only 40% (101/250) of the patients. Among this subgroup, 52% (53/101) had documented healthcare contact within or travel to the Indian subcontinent. Seven percent (7/101) had a history of travel to other countries, including Spain, Uganda, Kuwait, Egypt and the Democratic Republic of Congo; the country of travel was unavailable for two patients who nevertheless were reported to have travelled; 41% (41/101) of patients with data available were stated to have no history of travel.

Single NDM-positive isolates were received from 80% (201/250) of the patients and multiple isolates from the remaining 20% (49 patients). Amongst these latter patients with multiple NDM-positive isolates, 29% (16/49) had NDM-positive organisms of different species or genera. NDM-positive isolates were referred over periods of >6 months in 14% of patients (7/49) and for >1 year in two patients, but many patients had no follow-up isolates, precluding assessment of carriage duration. NDM-positive isolates were obtained from more than one anatomical site in 37% patients (18/49).

The date when the sample was taken was available for 87% (284/326) of isolates and the median duration between this date and the isolate being received at AMRHAI was 8 days (IQR 6–11 days).

Microbiology

The majority (94%, 306/326) of the NDM-positive isolates were Enterobacteriaceae, but 6% (20 isolates) were non-fermenters. Table 1 illustrates the details of source and species for the NDM-positive isolates for various settings. The commonest Enterobacteriaceae hosts were Klebsiella spp. (59%, 180/306) followed by E. coli (26%, 80/306). Acinetobacter spp. were the commonest non-fermenter hosts (80%, 16 isolates).

Most isolates (85%, 277/326) were from samples taken in hospital, but 13% (42/326) were from general practice urines; the setting was unavailable for 2% (7/326) of isolates. Thirty-eight percent of isolates from hospital settings were from urine specimens, with swabs contributing a further 32%. These swabs were divided fairly evenly between those from clinical sites and those taken for screening (49% versus 51%). Thirty-two (9.8%) of isolates were from blood cultures or line tips (Table 1).

Antibiotic susceptibility

MIC distributions for the Enterobacteriaceae and non-fermenters with NDM carbapenemases are shown in Table 2. Most NDM-positive bacteria were resistant or non-susceptible to all three carbapenems tested. However, two K. pneumoniae isolates and one Citrobacter koseri isolate were susceptible to imipenem, but with synergy still observed between this agent and EDTA. One isolate of Morganella morgani was susceptible to meropenem but resistant to both imipenem and ertapenem. Aztreonam susceptibilities were available for 67% (220/326) isolates, and only 12% (24/206) of the Enterobacteriaceae isolates tested were susceptible.

Resistence to all three aminoglycosides routinely tested (amikacin, gentamicin and tobramycin) was seen in 76% (234/306) of NDM-positive Enterobacteriaceae, but 18% were susceptible to at least one aminoglycoside and 6% to all three. High-level resistance (amikacin MICs >64 mg/L and gentamicin and tobramycin MICs >32 mg/L) was observed for 218 Enterobacteriaceae isolates. Similarly, 70% (14/20) of NDM-positive non-fermenters were resistant to the three aminoglycosides and 10 showed high-level resistance.

Most isolates were susceptible to colistin (90% of Enterobacteriaceae and 95% of non-fermenters). Susceptibility to ciprofloxacin varied from 12% to 15% according to species (Table 2).

Typing of the isolates

One hundred and seven out of 168 isolates of K. pneumoniae with NDM enzymes were typed by VNTR. After excluding isolates belonging to the same strain from a single patient, 85 results remained for analysis. In addition, a further 30 K. pneumoniae had been typed by PFGE. Most NDM-positive K. pneumoniae isolates represented either sporadic strains (27 unique types identified in total) or belonged to well-recognized international lineages (STs 11, 14, 15 and 17), which are prevalent generally and have been associated previously with other acquired carbapenemase genes (blaKPC, blaVIM or blaOXA-48). Isolates belonging to these lineages (which may have acquired blanDM repeated and separately) were received from multiple requestors with no epidemiological links apparent between many cases (Figure 2). The seven NDM-positive ST15 isolates from patients from a single hospital (Figure 2, ST15 cluster, hospital R) were received over a 17 month period, with no obvious
clustering in time. Nevertheless, there was an outbreak involving 14 patients in a urology clinic in 2010 (Figure 2, cluster A, hospital X; two additional isolates not shown in the figure were typed by PFGE). There were some other instances of epidemiologically linked cases, where cross-infection was likely, as noted previously.10 One patient was found to have two distinct \textit{K. pneumoniae} strains each carrying \textit{bla}_{NDM}.

Typing data (PFGE) were also available for 37 non-duplicate \textit{E. coli} isolates. Most (65%, 24/37) were unique, but three clusters were identified, one of which consisted of isolates from eight patients from six different, geographically distant hospitals (Figure 3). This cluster corresponds to ST636. Two other pairs of isolates shared similar PFGE profiles, but in each case they were separated in both time and space.

For the remaining genera, only limited numbers of isolates were typed. While there were some examples of strains being shared by several patients (affecting two to five patients in the same centre), most isolates appeared to be sporadic. The four \textit{NDM}-positive \textit{P. aeruginosa} isolates were from different hospitals and represented distinct strains. Three belonged to international lineages associated with metallo-\beta-lactamases (STs 654, 111 and 357); the fourth (VNTR profile 10,2,7,3,6,1,8,5,6) had a \textit{bla}_{VIM} allele in addition to \textit{bla}_{NDM}.

**Discussion**

This report reviews the first 250 cases affected (infected or colonized) by \textit{NDM}-positive bacteria in the UK, as ascertained from referrals to PHE’s national reference laboratory. They were recognized over a period of 5.5 years from February 2008 to July 2013. As such, this analysis presents data for the largest ‘national’ collection of \textit{NDM}-positive isolates so far reported outside the Indian subcontinent.

![Figure 3. PFGE profiles of XbaI-digested genomic DNA from \textit{NDM}-positive isolates of \textit{E. coli} received between 2008 and July 2013 from 29 patients, showing clusters of isolates (1–3). Isolates were from hospitals A–V; N is the only hospital shared with Figure 2. The line defining clusters is at 86% similarity.](https://academic.oup.com/jac/article-abstract/69/7/1777/2911229)
The majority of isolates were from male patients and from those >60 years of age. This contrasts with isolates reported from India by Kumarasamy et al.,\textsuperscript{10} where the majority of patients were females with a mean age of 36 years. Isolates were primarily from urine specimens (47%, 152/326), and all the isolates from primary care were from urine; other frequent sources included clinical and screening swabs, and bacteraemia. A study from a tertiary care hospital in north-east India screened 270 isolates of \textit{E. coli} for carbapenemases and identified 14 isolates positive for \textit{bla}_{NDM} and there, too, the majority of the isolates were urinary (10/14) and 57% (8/14) were from male patients.\textsuperscript{23}

Although crude travel history data were available for only 40% of our patients, about half of these had travelled to or had healthcare contact in the Indian subcontinent. Individual patients had also travelled to countries in central Africa (Democratic Republic of Congo and Uganda), the Middle East (Egypt and Kuwait) and Spain. None of these 250 patients had known links to the Balkans, which is suggested to be a second epicentre for \textit{NDM-positive bacteria}.\textsuperscript{5} Of concern, >40% of the patients for whom crude travel data were supplied were stated to have no history of foreign travel. We also noted a substantial number of \textit{NDM-positive bacteria} from patients treated in primary care. The age range affected suggests that many may have had previous healthcare contact, but clearly \textit{NDM-positive bacteria} may be found in the community. ‘\textit{NDM cases}’ without prior contact with healthcare settings have been reported elsewhere.\textsuperscript{24,25}

The molecular epidemiological knowledge gained so far about \textit{NDM-positive isolates} provides evidence both for gene spread between plasmids with different replicon types and for plasmid spread between different strains, species and genera.\textsuperscript{5} There is much less evidence for extensive dissemination by high-risk clones, whereas the spread of \textit{KPC carbapenemase} is strongly linked to dissemination of \textit{K. pneumoniae} ST258 and its variants. In this report, 29% (14/49) of patients with multiple \textit{NDM-positive isolates} had isolates of different species or genera. In some instances it was possible to demonstrate shared plasmids in such cases (J. Findlay, K. L. Hopkins and N. Woodford, unpublished data), but the direction of transmission cannot be inferred, nor can one draw firm conclusions about transfer events within the affected patient; some patients may have been colonized by multiple \textit{NDM-positive strains} or species at source. Typing of the isolates, where available, revealed one outbreak of \textit{NDM-positive K. pneumoniae} involving 14 patients and identified three clusters of \textit{E. coli}, though most of the \textit{E. coli} isolates within these latter clusters did not appear to be epidemiologically linked.

Most of the isolates were resistant to all carbapenems tested and all showed potentiation of imipenem by EDTA, confirming MBL activity. Although aztreonam is not inactivated by \textit{NDM} (or other metallo-enzymes), 88% (182/206) of the \textit{Enterobacteriaceae} isolated tested were resistant, as is frequently the case elsewhere,\textsuperscript{10,23} almost certainly reflecting the presence of multiple resistance mechanisms, such as ESBLS and AmpC enzymes.

Among non-\textit{β-lactams}, ciprofloxacin resistance was seen in 87% (285/326) of \textit{NDM-positive isolates}. High-level resistance to the three aminoglycosides tested was seen in 71% (218/306) of \textit{Enterobacteriaceae} and in 50% (10/20) of non-fermenters. This may reflect the production of one or more 16S rRNA methyltransferases. In a recent study,\textsuperscript{26} isolates with both \textit{NDM} enzymes and 165 rRNA methyltransferases, including the novel \textit{RmtF} enzyme, were described. The majority of our \textit{NDM} isolates were susceptible to colistin (90%, 295/326) and tigecycline (57%, 187/326), as also noted in other studies.\textsuperscript{10,11} Nevertheless, colistin use may lead to development of resistance during therapy\textsuperscript{11} and is potentially nephrotoxic and neurotoxic. Tigecycline is licensed for complicated abdominal and skin and soft tissue infections and may not be a suitable agent for treating urinary tract infections owing to low urinary concentrations.\textsuperscript{11} In this report, all isolates obtained from primary care settings were urinary, posing a therapeutic challenge.

Prolonged carriage of \textit{NDM-positive isolates} has been reported previously.\textsuperscript{27,28} Here, we found instances of apparent carriage for >6 months in 14% (7/49) of patients with multiple isolates. Positive isolates were identified >1 year apart in two cases. Such patients may act as a reservoir for the spread of \textit{NDM-positive bacteria} in the hospital and community setting.

The major limitation of our data is the paucity of clinical details about the patients, including treatments prescribed and outcomes. However, we have summarized available epidemiological and typing data for 250 cases and 326 \textit{NDM-positive isolates} identified over 5.5 years in the UK. The dissemination of \textit{NDM enzymes} among diverse strains, species and genera of \textit{Enterobacteriaceae} and non-fermenters and their frequent multidrug resistance is clearly demonstrated, with most cases being sporadic. This report highlights: the need to find effective therapeutic options; the need for rapid and robust diagnostic tools to aid accurate and prompt identification of \textit{NDM-positive isolates}; the desirability of strengthening current surveillance programmes; the need for international collaboration; and, last but not least, the continuing need for infection prevention and control processes to limit transmission within healthcare settings.

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Transparency declarations

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