

## GLOBAL HEALTH

## Trends in the Indications for Corneal Graft Surgery in the United Kingdom

1999 Through 2009

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**Objective:** To examine trends in the indications for corneal graft surgery in the United Kingdom.

**Methods:** National Health Service Blood and Transplant data were analyzed for keratoplasty operations performed in the United Kingdom between April 1, 1999, and March 31, 2009, distinguishing the type of graft and the surgical indication.

**Results:** The total number of annual keratoplasty operations increased from 2090 in 1999-2000 to 2511 in 2008-2009. Among these, the annual number of grafts performed for endothelial failure increased from 743 (35.6%) in 1999-2000 to 939 (37.4%) in 2008-2009. The performance of penetrating keratoplasty (PK) for endothelial failure decreased from 98.3% of all grafts in 1999-2000 to 46.6% of all grafts in 2008-2009, while the performance of endothelial keratoplasty increased from 0.3% of all grafts in 1999-2000 to 51.2% of all grafts in 2008-2009. The annual number of grafts performed for keratoconus increased from 514 (24.6%) in 1999 to 564 (22.5%) in 2008-2009. The performance of PK for keratoconus decreased from 88.4% of all grafts in 1999-

2000 to 57.1% of all grafts in 2008-2009, while the performance of deep anterior lamellar keratoplasty increased from 8.8% of all grafts in 1999-2000 to 40.1% of all grafts in 2008-2009. The number of annual regrant operations increased from 249 (11.9%) in 1999-2000 to 401 (16.0%) in 2008-2009, most commonly for endothelial failure. In 2008-2009, PK regrafts (78.1%) far outnumbered endothelial keratoplasty regrafts (17.0%).

**Conclusions:** Endothelial failure is the most common indication for keratoplasty in the United Kingdom, and endothelial keratoplasty is performed more commonly than PK for this indication. The number of grafts performed for pseudophakic bullous keratopathy has remained stable, while the number of grafts performed for Fuchs endothelial dystrophy is likely to continue increasing. Keratoconus is the second most common indication for keratoplasty, and deep anterior lamellar keratoplasty numbers are approaching those for PK. Regraft surgery is the third most common indication for keratoplasty, required in most cases because of endothelial failure.

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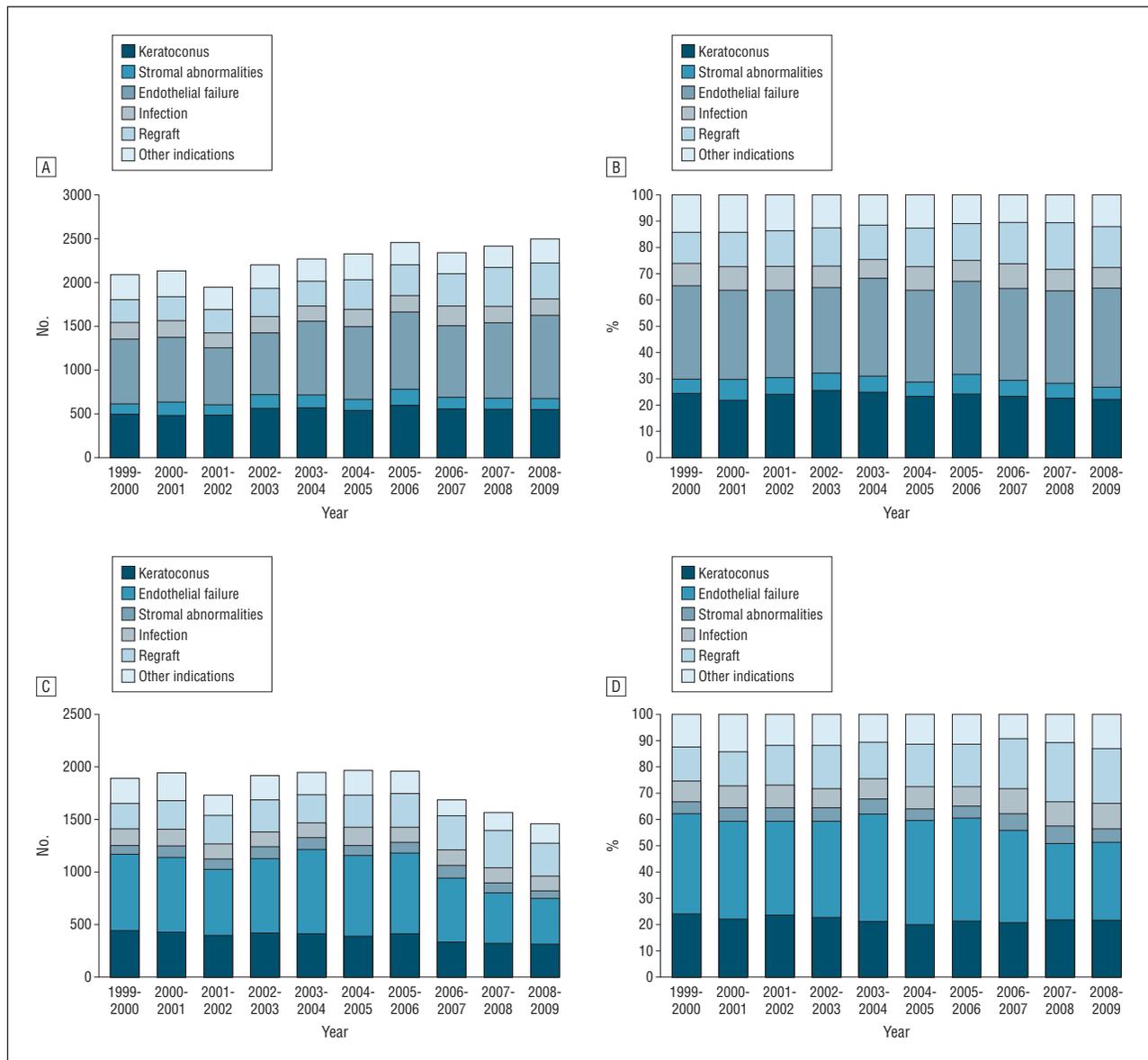
**Group Information:** Members of the National Health Service Blood and Transplant Ocular Tissue Advisory Group and Contributing Ophthalmologists (Ocular Tissue Advisory Group Audit Study 8) are listed at the end of the article.



CORNEAL GRAFT SURGERY IS performed for a wide variety of indications, including corneal ectasias, stromal abnormalities, endothelial failure, and primary graft failure or rejection. The prevalences of corneal diseases may have changed during recent years, particularly with shifts in population demographics and changes in ophthalmological practice. For example, the prevalence of Fuchs endothelial dystrophy (FED) may have increased in the United Kingdom given its aging population,<sup>1</sup> while the incidence of pseudophakic bullous keratopathy (PBK) may have changed substantially following the introduction and continuing refinement of

phacoemulsification cataract surgery.<sup>2-4</sup> Therefore, the numbers of patients requiring corneal graft surgery for different indications may have changed considerably in recent years, while the last published study<sup>5</sup> of indications for corneal graft operations throughout the United Kingdom covered the decade from 1990-1991 to 1999-2000 and pertained only to penetrating keratoplasty (PK).<sup>5</sup>

The past decade has seen the increased use of lamellar keratoplasty for some surgical indications, in the form of anterior lamellar keratoplasty and endothelial keratoplasty (EK). While the total number of corneal graft operations performed annually in the United Kingdom has risen slowly over the past decade, the proportion of lamellar keratoplasty



**Figure 1.** Annual numbers and proportions of keratoplasties under the Corneal Transplant Service in the United Kingdom, subdivided by indication. A and B, All keratoplasty operations. C and D, Penetrating keratoplasty.

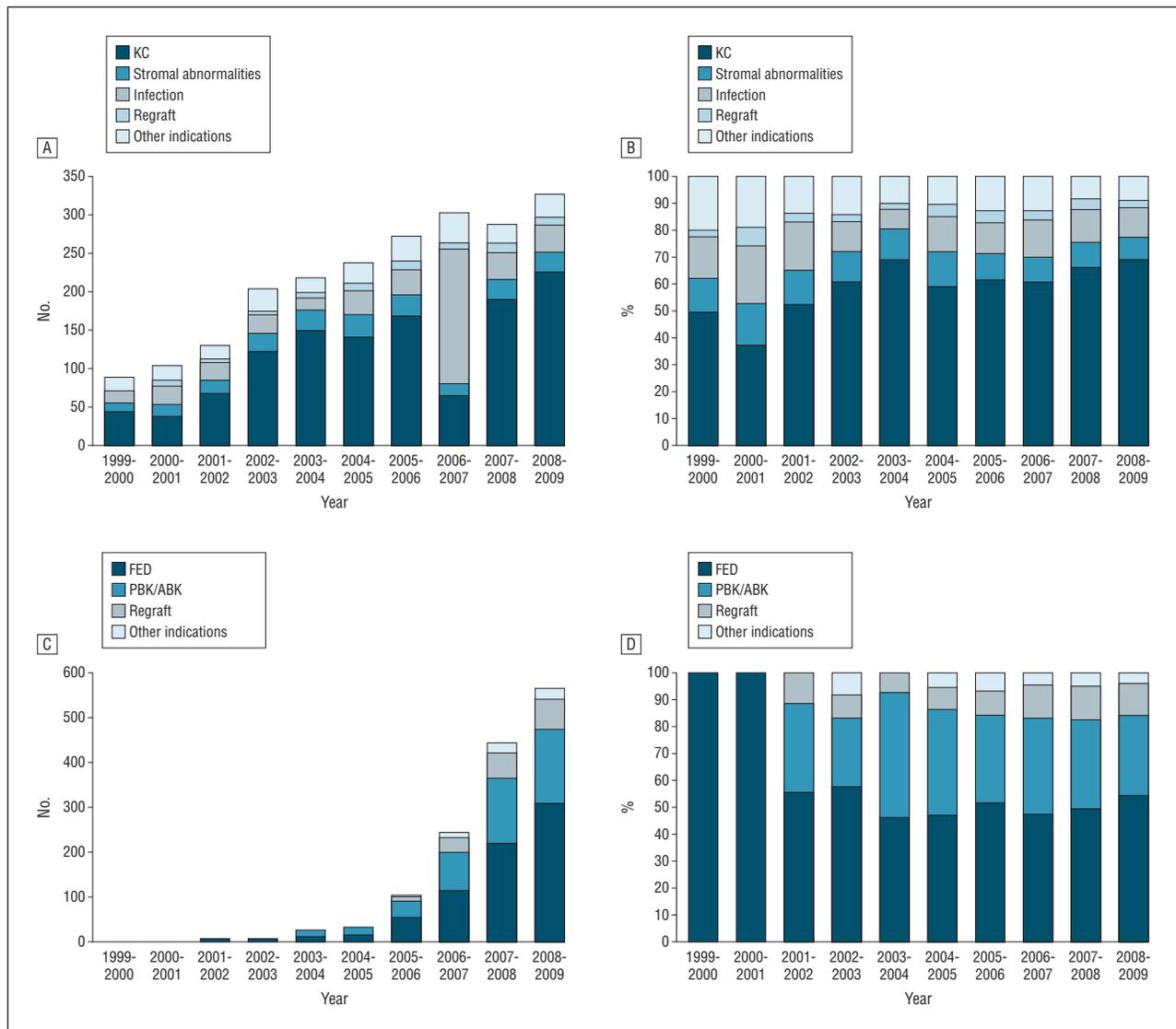
vs PK cases has increased substantially.<sup>6</sup> Annual PK operations under the National Health Service Blood and Transplant (NHSBT) decreased from 1901 in 1999-2000 to 1473 in 2008-2009; during the same period, deep anterior lamellar keratoplasty (DALK) operations increased from 91 to 327 per year, and EK operations increased from 2 to 569 per year.<sup>6</sup>

To date, no published data are available on the proportions of keratoconus operations performed using PK vs DALK during the past decade in the United Kingdom or on the proportions of patients with FED or PBK undergoing PK vs EK. In the context of finite supplies of corneal tissue, it is useful to have accurate data on past and current practices in corneal graft surgery to predict future requirements, particularly of lamellar vs full-thickness grafts. Therefore, the objective of this study was to examine trends in the numbers and proportions of corneal graft operations in the United Kingdom during the past decade by the type of graft and the surgical indication.

## METHODS

The annual numbers of eyes undergoing corneal graft surgery in the United Kingdom were calculated from NHSBT data for the period April 1, 1999, to March 31, 2009, distinguishing PK, DALK, EK, and other keratoplasty. As described previously,<sup>6</sup> this data set is composed of information collected by the NHSBT through the transplant record form. It includes data on patients receiving donor corneal material supplied by the 2 Corneal Transplant Service (CTS) eye banks (Manchester Eye Bank, Manchester, England, and Bristol Eye Bank, Bristol, England). The accuracy of the data set is dependent on completion and return of transplant record forms by every center performing corneal graft surgery, but the NHSBT Ocular Tissue Transplant Audit<sup>7</sup> demonstrated a return rate of 97% during the study period.

The annual numbers of eyes undergoing corneal graft surgery through the CTS were classified by surgical indication into the following categories: keratoconus, stromal abnormalities (comprising stromal dystrophy and stromal opacification), en-



**Figure 2.** Annual numbers and proportions of keratoplasties for keratoconus under the Corneal Transplant Service in the United Kingdom, subdivided by indication. A and B, Deep anterior lamellar keratoplasty. C and D, Endothelial keratoplasty. ABK indicates aphakic bullous keratopathy; FED, Fuchs endothelial dystrophy; and PBK, pseudophakic bullous keratopathy.

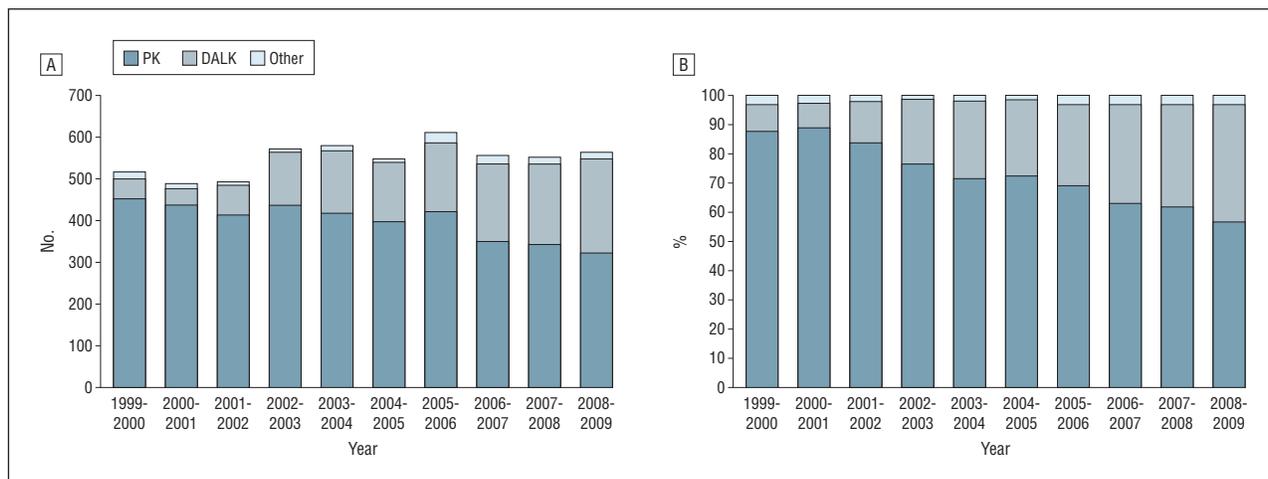
dothelial failure (comprising FED, PBK, and aphakic bullous keratopathy [ABK]), infection (comprising viral, bacterial, fungal, protozoan, and other infection), regraft, and other indications. For each indication, the annual numbers and proportions of eyes undergoing PK, DALK, EK, or other keratoplasty were calculated. Where proportions of grafts were compared at different time points, the  $\chi^2$  test was used. Statistical analysis was performed using commercially available software (SAS version 9.1 software; SAS Institute, Inc).

## RESULTS

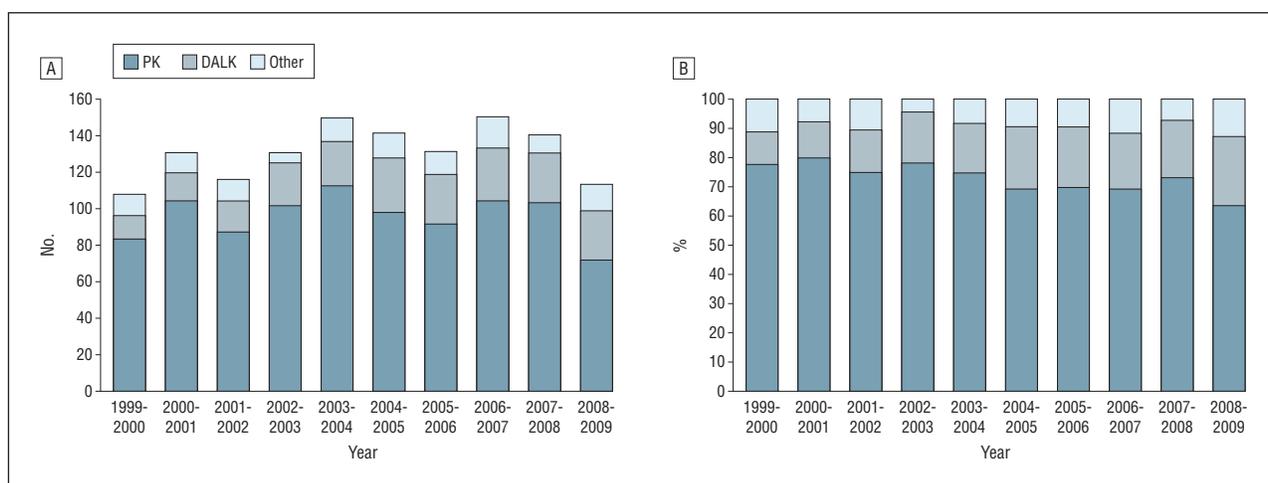
The annual numbers of corneal graft operations performed in the United Kingdom under the NHSBT, subdivided by indication, are shown in **Figure 1A** and **B**. The total number of operations increased from 2090 in 1999-2000 to 2511 in 2008-2009. The annual number of operations for keratoconus increased from 514 in 1999-2000 to 608 in 2005-2006 and then decreased modestly to a plateau of about 550 (2006-2007 to 2008-2009). How-

ever, the proportion of grafts performed for keratoconus remained constant during the study period at about 25%. The number of operations for stromal abnormalities fluctuated between 108 in 1999-2000 and 150 in 2006-2007, accounting for approximately 6% of all grafts during the study period. The annual number of grafts performed for endothelial failure increased substantially from 743 in 1999-2000 to their highest level of 939 in 2008-2009, representing from 34.2% of all grafts in 2000-2001 and 37.4% of all grafts in 2008-2009 ( $P = .06$ ). The number of grafts performed for infection remained stable at about 190 per year (7.6% of all grafts in 2008-2009). In contrast, the annual number of regraft operations increased substantially from 249 (11.9%) in 1999-2000 to 401 (16.0%) in 2008-2009 ( $P < .001$ ).

The annual numbers and proportions of PK operations, subdivided by indication, are shown in **Figure 1C** and **D**. Results are also shown for DALK (**Figure 2A** and **B**) and for EK (**Figure 2C** and **D**).



**Figure 3.** Annual numbers (A) and proportions (B) of keratoplasties for stromal abnormalities under the Corneal Transplant Service in the United Kingdom, subdivided by type of graft. DALK indicates deep anterior lamellar keratoplasty; PK, penetrating keratoplasty.



**Figure 4.** Annual numbers (A) and proportions (B) of keratoplasties for stromal abnormalities under the Corneal Transplant Service in the United Kingdom, subdivided by type and graft. DALK indicates deep anterior lamellar keratoplasty; PK, penetrating keratoplasty.

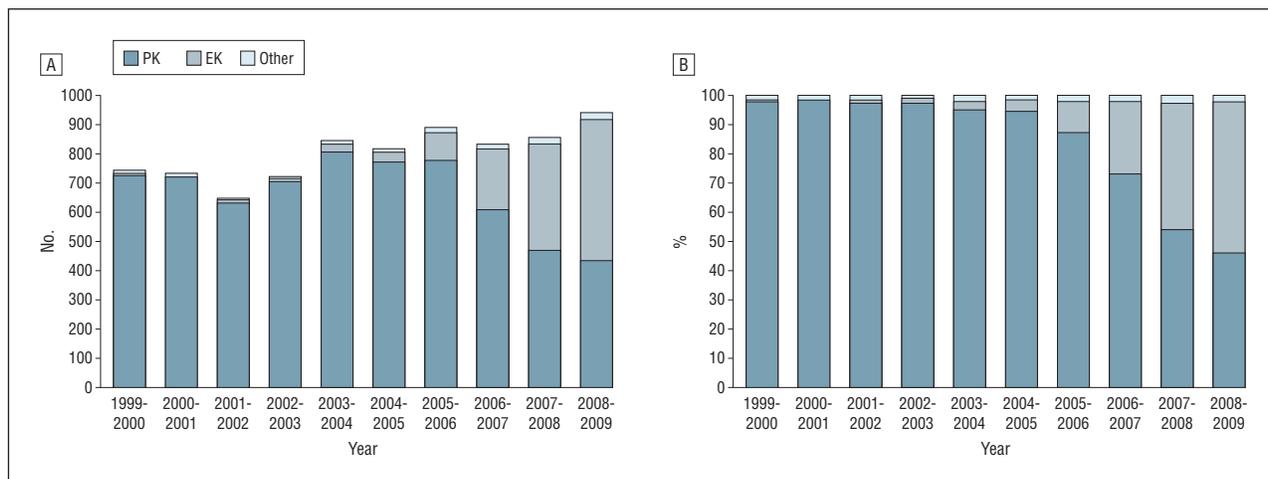
The annual numbers and proportions of eyes undergoing PK vs DALK in the United Kingdom for keratoconus are shown in **Figure 3**. The number of PK operations decreased gradually during the past decade from 453 in 1999-2000 to the lowest level of 322 in 2008-2009. In contrast, the number of DALK operations increased more than 5-fold, from 45 in 1999-2000 to 226 in 2008-2009. Expressed as a proportion of the total number of grafts for keratoconus, this represents a decrease from 88.1% in 1999-2000 to 57.1% in 2008-2009 for PK and an increase from 8.8% in 1999-2000 to 40.1% in 2008-2009 for DALK ( $P < .001$ ).

Results for eyes undergoing keratoplasty for stromal abnormalities are shown in **Figure 4**. The annual number of PK operations fluctuated during the past decade between 72 and 112. In contrast, the number of DALK operations more than doubled during 5 years, from 12 in 1999-2000 to 30 in 2004-2005 and has since remained at a plateau of about 28 per year. Expressed as a proportion of the total number of grafts for stromal abnormalities, this represents a decrease from 77.8% in 1999-2000 to 63.7% in 2008-2009 for PK and an increase from

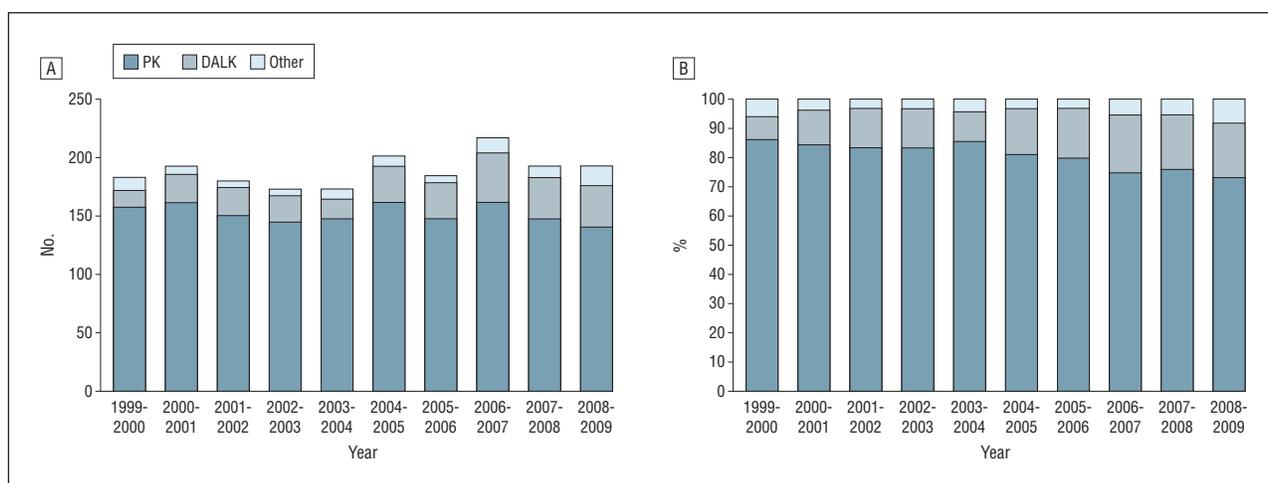
11.1% in 1999-2000 to 23.9% in 2008-2009 for DALK ( $P = .03$ ).

Similarly, results for endothelial failure are shown in **Figure 5**. The number of PK operations fluctuated between 633 in 1999-2000 and 805 in 2005-2006, and it decreased rapidly from 777 in 2005-2006 to the lowest level of 438 in 2008-2009. In contrast, the number of EK operations increased roughly exponentially from 2 in 1999-2000 to 95 in 2005-2006 and then more linearly to the highest level of 481 in 2008-2009. This represents for PK a halving from 98.3% of all grafts for endothelial failure in 1999-2000 to 46.6% in 2008-2009, and it represents for EK an increase from 0.3% of all grafts for endothelial failure in 1999-2000 to 51.2% in 2008-2009 ( $P < .001$ ). Hence, for the first time in 2008-2009, EK was performed more commonly than PK for eyes with endothelial failure. Trends by graft type for endothelial failure were similar to those for its individual component indications (FED, PBK, or ABK), as discussed in the "Comment" section.

Results for eyes undergoing keratoplasty for infection are shown in **Figure 6**. The number of PK opera-



**Figure 5.** Annual numbers (A) and proportions (B) for keratoplasties for endothelial failure under the Corneal Transplant Service in the United Kingdom, subdivided by type of graft. EK indicates endothelial keratoplasty; PK, penetrating keratoplasty.



**Figure 6.** Annual numbers (A) and proportions (B) of keratoplasties for infection under the Corneal Transplant Service in the United Kingdom, subdivided by type of graft. DALK indicates deep anterior lamellar keratoplasty; PK, penetrating keratoplasty.

tions varied from 144 in 1999-2000 to 165 in 2006-2007, and then it decreased from 162 (75.0% of all grafts for infection) in 2006-2007 to 140 (72.9%) in 2008-2009 ( $P=.63$ ). During the same period, the number of DALK operations more than doubled, from 14 (7.7%) in 1999-2000 to 36 (18.8%) in 2008-2009 ( $P=.002$ ).

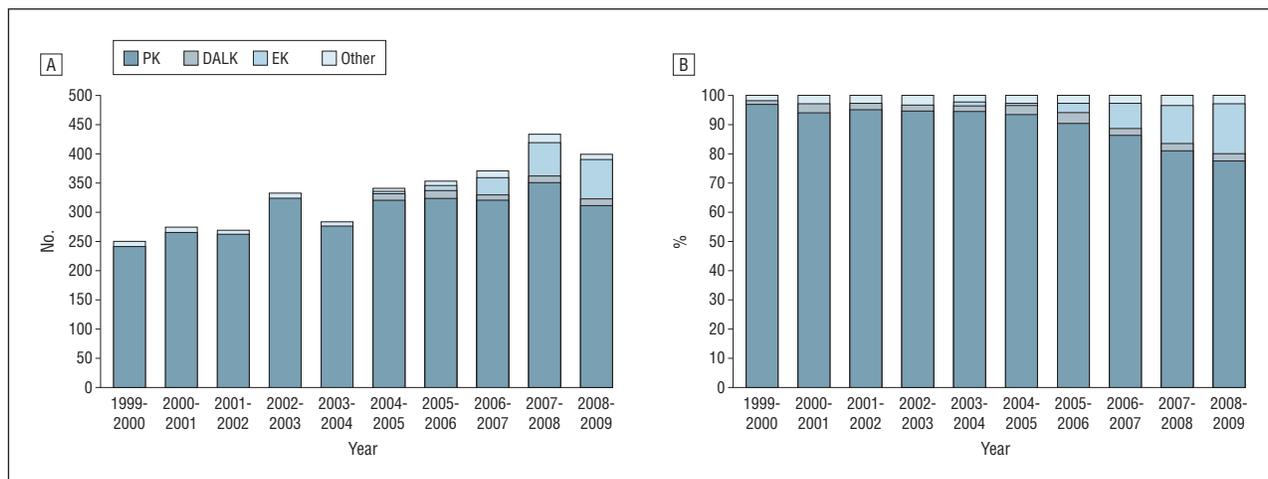
Results for eyes undergoing regrant keratoplasty are shown in **Figure 7**. Most of the increase in regrant operations during the past decade was accounted for by an increase in the number of regrants as PK operations, from 243 (97.6% of all regrants) in 1999-2000 to 313 (78.1%) in 2008-2009 ( $P<.001$ ). However, the number of regrants as EK operations also contributed in the later years, increasing from 1 (0.4%) in 2001-2002 to 68 (17.0%) in 2008-2009 ( $P<.001$ ), while few regrants as DALK operations were performed during the study period.

#### COMMENT

Keratoplasty for keratoconus has continued during the past decade to represent about one-quarter of the total corneal graft workload in the United Kingdom. This proportion is

similar to that published for CTS grafts in the previous decade (1990-1999), when a mean of 24% (range, 19%-27%) of annual PK operations were performed for keratoconus.<sup>5</sup> Our data demonstrate that the performance of PK for keratoconus has gradually decreased during the past decade, while the performance of DALK has increased substantially and now accounts for more than 40% of keratoplasty operations for keratoconus. Indeed, in 2008-2009, more than two-thirds of DALK operations were performed for keratoconus. There is no evidence from these data that the graft requirement for keratoconus has decreased with the advent of intracorneal ring implantation<sup>8</sup> or collagen cross-linking.<sup>9,10</sup>

DALK techniques continue to evolve, and an ongoing debate exists about visual and survival outcomes associated with PK vs DALK for keratoconus.<sup>11-15</sup> It is notable that 2004-2005 saw a temporary reduction in DALK operations for keratoconus (from 152 to 142,  $P=.88$ ), while 2005-2006 saw the opposite trend for PK (from 398 to 421,  $P=.21$ ). This suggests that some corneal surgeons may temporarily have reverted to PK instead of DALK for keratoconus, most likely following concerns



**Figure 7.** Annual numbers (A) and proportions (B) of regrant keratoplasty operations under the Corneal Transplant Service in the United Kingdom, subdivided by type of graft. EK indicates endothelial keratoplasty; DALK, deep anterior lamellar keratoplasty; and PK, penetrating keratoplasty.

that interface opacification may limit visual outcomes in DALK.<sup>16</sup> However, a recent meta-analysis<sup>11</sup> of studies comparing DALK and PK found that the 2 techniques were equivalent for the outcome measure of best-corrected visual acuity and that DALK was superior to PK for the preservation of endothelial cell density. A further advantage of DALK is the absence of any endothelial immune graft rejection, which may improve long-term graft performance; however, improved graft survival with DALK has not yet been demonstrated, and further studies may help determine relative visual and survival outcomes in DALK vs PK as best practiced.

Keratoplasty for endothelial failure has increased during the past decade and continues to represent more than one-third of the total corneal graft workload in the United Kingdom. Corneal Transplant Service data showed that between 1990 and 1999 approximately one-quarter of PK operations were performed for endothelial failure.<sup>5</sup> Our data for the most recent decade (1999-2009) demonstrate that the proportion of all grafts performed for endothelial failure has gradually increased further to 37% in 2008-2009. In particular, the annual number of grafts for FED increased substantially from 361 (17.3% of all grafts) in 1999-2000 to 559 (22.3%) in 2008-2009. During the same period, the number of grafts for PBK was stable at about 320 (14%), while the number of grafts for ABK decreased from 65 (3.1%) in 1999-2000 to 27 (1.1%) in 2008-2009. Compared with the percentages of PK operations by the CTS from 1990 to 1999, before the advent of EK in the United Kingdom, surgery for FED was already increasing, from 8% of PK operations in 1990 to 13% of PK operations in 1999; PBK represented about 8% of PK operations, while ABK decreased from 13% of PK operations in 1990 to 2% of PK operations in 1995 through 1998, a substantial reduction.<sup>5</sup>

The number of eyes requiring keratoplasty for FED is likely to increase further over time given the aging population of the United Kingdom. The number of eyes requiring keratoplasty for PBK remained stable during the past decade. It seems likely that the substantial increase in the rate of patients undergoing cataract surgery in the United Kingdom<sup>17</sup> may be influenced by ongoing im-

provements in phacoemulsification technology and endothelial protection.<sup>3,4,18,19</sup> However, it will be important to continue studying trends in the numbers of patients requiring surgery for FED and PBK during the next decade because this will have implications for the numbers of EK and PK grafts required in future years for transplantation.

Indeed, our data show that endothelial failure is the most common indication for any keratoplasty, as well as for PK and EK. Furthermore, the rapid decrease in PK for endothelial failure from 2005-2006 onward was mirrored by a substantial increase in EK, suggesting that many corneal surgeons switched technique for appropriate patients at this time. Hence, EK is performed more commonly than PK for eyes with endothelial failure, and the National Institute for Health and Clinical Excellence<sup>20</sup> reported in 2009 that current evidence on safety and efficacy was adequate to support the use of EK based on the combined results of more than 6000 operations. The potential advantages and disadvantages of EK have been described previously,<sup>6,21</sup> and ongoing studies comparing the visual and survival outcomes of EK vs PK grafts will be important in informing the ongoing debate.

The performance of keratoplasty following all causes of corneal infection remained stable during the past decade, representing about 8% of all corneal graft surgery in the United Kingdom. The annual number of grafts performed following viral infection decreased significantly from 108 (5.2% of all grafts) in 1999-2000 to 84 (3.3%) in 2008-2009 ( $P = .002$ ), while the annual number of grafts performed following bacterial infection increased from 47 (2.2%) in 1999-2000 to 73 (2.9%) in 2008-2009 ( $P = .16$ ). Likely explanations for this include improved treatment with antiviral agents, particularly for herpes simplex virus,<sup>22</sup> and increased incidence of bacterial keratitis from contact lens wear.<sup>23,24</sup> Indeed, the proportion of CTS PK operations performed for viral keratitis showed a downward trend (from 6% in 1990-1991 to 2% in 1998-2009) in the previous decade.<sup>5</sup> Our data demonstrate that the number of PK operations for corneal infection decreased from 2006 to 2007, while the number of DALK operations for corneal infection increased gradually, sug-

gesting that some surgeons switched technique around this time for some patients. Indeed, the largest recent United Kingdom study<sup>25</sup> of DALK for herpetic corneal scarring showed comparable visual outcomes and better graft survival rates compared with PK.

Regraft keratoplasty has increased during the past decade and accounts for 15% of corneal graft activity in the United Kingdom. This percentage is similar to the 18% reported in the Corneal Transplant Follow up Study<sup>26</sup> from 1981 to 1991 for the United Kingdom and Republic of Ireland. Among all regrafts performed in 2008-2009, PK operations (78%) far outnumbered EK operations (17%), while few DALK regrafts (3%) were performed. Endothelial failure was the most common indication for re-graft surgery, which increased substantially during the past decade, from 70 regrafts in 1999-2000 to 166 regrafts in 2008-2009; this rise was accounted for by an increase in PK regrafts (from 69 in 1999-2000 to 113 in 2008-2009) and by a substantial increase in EK regrafts (from 3 in 2005-2006 to 47 in 2008-2009). Graft rejection was the second most common indication for re-graft surgery, accounting for about 85 operations per year during the past decade. Recent research has demonstrated that for keratoconus PK is associated with a higher incidence of rejection than DALK; however, this is largely accounted for by endothelial rejection because the frequencies of epithelial rejection (5.2% for PK vs 4.2% for DALK) and stromal rejection (4.8% for PK vs 6.3% for DALK) were similar between graft types.<sup>15</sup>

Ghosheh et al<sup>27</sup> examined trends in PK, EK, and anterior lamellar keratoplasty from 2001 to 2005 in the United States, including an analysis of indications, but this study was limited to one tertiary referral center. Darlington et al<sup>28</sup> reported trends in keratoplasty from 1980 to 2004 throughout the United States, including an analysis of indications, but this study was limited to PK. The authors found that the total number of PK operations performed in the United States (using corneas from study eye banks) declined steadily from 1990 to 2004. Their analysis of trends revealed that the population rate of PK for PBK decreased significantly from 1990 to 2004, as did that for ABK, while the rates for FED, keratoconus, and re-graft increased significantly. In that study, the most common indication in 2004 for PK was PBK (20%), followed by ectasias (15%), primary endotheliopathies (14%), and regrafts (11%).

The present study is limited by several aspects of the data set and methods, but attempts were made throughout to minimize these limitations. As already described, the NHSBT data set contains information on patients receiving donor corneas from the 2 CTS eye banks. However, during the study period, the data set did not capture information from the few patients (about 10%) receiving grafts from other eye banks, including Moorfields Eye Bank, London, England, and East Grinstead Eye Bank, East Grinstead, England. Also, the accuracy of data relies on correct completion of transplant record forms by individuals at all corneal centers, and completeness of the data set is dependent on the return of all forms. Reassuringly, the NHSBT Ocular Tissue Transplant Audit<sup>7</sup> demonstrated a return rate of 97% during the study period. Finally, transplant record

form coding and data compilation may lead to some loss of useful information. The methods used herein enabled us to distinguish between PK, DALK, and EK as re-graft operations, but we were unable to determine the nature of the primary operation (ie, lamellar or full thickness).

To our knowledge, this is the first comprehensive study of recent trends in corneal graft surgery performed throughout a country, including analyses by the type of graft and the surgical indication, since the advent of lamellar keratoplasty. In the United Kingdom, the numbers of patients requiring corneal graft surgery for different indications have changed substantially during the past decade: endothelial failure is the most common indication for keratoplasty, and EK is performed more commonly than PK for this indication. Keratoconus is the second most common indication for keratoplasty, and DALK numbers are approaching those for PK. Changes in population demographics and ophthalmological practice in developed countries are clearly influencing the annual numbers of keratoplasty operations required at present and in the future. These data have important implications for corneal surgeons in practice and in training and will enable eye banks to plan their activity for the decades to come.

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**Author Contributions:** Dr Keenan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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