


SHORT COMMUNICATION

An outbreak of adenovirus D8 keratoconjunctivitis in Leicester, United Kingdom, from March to August 2019

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Abstract

We report a large epidemic ($n = 126$) of keratoconjunctivitis predominantly with two lineages of adenovirus (AdV) type D8 in patients seen in eye casualty between march and August 2019. Other AdV species identified by viral sequencing included B, C, and E. Despite various features of more severe eye disease being present, these were not significantly different between the different AdV species, with similar rates of pseudomembrane formation and keratitis observed in patients with AdV species B as for those with AdV species D.

KEYWORDS

adenovirus, community, incidence, keratoconjunctivitis, nosocomial, outbreak, transmission, UK

1 | INTRODUCTION

Human adenoviruses (AdVs) cause numerous and varying infections in humans of all ages worldwide and are recognized as the most common cause of infectious conjunctivitis.¹ AdV conjunctivitis is highly contagious and spreads by person to person contact particularly with behaviors such as touching eyes with uncleaned hands, applying makeup, sharing towels and pillow cases, or communal bathing. Patients are contagious for as long as the eye is red. AdV conjunctivitis is seen throughout the year and can occasionally cause large epidemic keratoconjunctivitis (EK) outbreaks, most frequently caused by the human mastadenovirus species D.² Outbreaks in healthcare facilities often arise from inadequate cleaning of medical equipment and can quickly lead to large numbers of cases.³ Epidemics of keratoconjunctivitis frequently become centered around healthcare facilities as a result. AdV is a robust virus which can transfer to surfaces easily, survive there for several hours, and resist cursory cleaning methods such as alcohol.⁴ A patient with AdV keratoconjunctivitis rubbing their sore eyes can quickly contaminate

the environment widely, and, therefore, infect other patients and staff in the department.

A recent review from the United States of America of AdV conjunctivitis cases reported some seasonal variation, with the highest number of cases being seen during July–September, and the lowest during April–June.⁵ Similar data are not available for the UK where AdV reporting is patchy without a centralized national system for monitoring the incidence of eye infections that are available in some countries such as Japan and Germany.^{6–9} Indeed, it has been some time since an outbreak of EK in the United Kingdom has been reported.^{10–12}

2 | MATERIALS AND METHODS

In June 2019, clinical colleagues in eye casualty notified the virology team about an unusual increase not only in the number of AdV conjunctivitis cases being seen but also in their severity. Thirty-eight cases required 2–5 follow-up appointments at an interval of 2–4

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weeks due to more serious diseases, such as pseudomembrane formation (PF), which is a recognized complication seen in EK. This can, in turn, lead to persistent corneal irritation and inflammation and dry eye(s), which can lead to mild symblepharon, where the eyelid conjunctiva adheres to the bulbar conjunctiva.

Eye swabs are routinely received for virology testing in viral transport medium and diagnostic polymerase chain reaction assays are performed to look for herpes simplex-1 (HSV-1) and HSV-2, varicella-zoster virus, and AdV, using a combination of in-house¹³ and commercial assays (Ausdiagnostics UK Ltd.). In response to this apparent and unexpected rise in the number of cases of AdV EK, we reviewed all our recent AdV positive eye swab results for the previous 3 months, then compared these to the number of AdV positive samples over the previous 5 years to assess whether this was likely to be a true outbreak.

Further viral sequencing and typing of these AdV positive eye swabs were arranged with the Public Health England (PHE) Reference Laboratory. In addition, the ophthalmology team reviewed the clinical notes for all the AdV-infected patients, to assess whether this outbreak AdV strain was significantly associated with more clinically severe disease.

To determine if the more severe disease was more commonly associated with a specific AdV type, the ophthalmology team performed a blinded (to the AdV type) review of all the AdV positive cases. The clinical profiles of these patients were then matched to the AdV type once these results were available. The categories of severe AdV eye disease were categorized as follows: unilateral versus bilateral complicated disease: keratitis, specific superficial punctate keratitis (SPK), PF, and/or punctate epithelial erosions (PEE). With no recognized scale for comparing the severity of these effects, the ophthalmology team only assessed for the presence or absence of these complications without grading, and so forth.

For the analysis of these results, we started with the null hypotheses that there was no one species responsible for the outbreak

and that there was no difference in the severity of eye disease seen between the different AdV types detected during the course of the outbreak period. Given the small sample size of identified AdV types ($n = 48$), we were aware that an effect would likely only be detected if there was a very large difference between them. For each AdV type, we assessed whether there was bilateral disease and the presence or absence of the complications listed above as assessed for all 48 patients.

3 | RESULTS

Figure 1 shows that while there have been sporadic cases throughout most years, the sudden rise in the number of cases during March–June 2019 is unusual. During the previous 5-year period (2014–2018), the average number of confirmed positive AdV conjunctivitis cases by the end of June has been approximately 41. The total number of cases seen from January 2019 to the end of June 2019 has been 112 (Figure 2).

In addition, the number of severe cases of AdV keratoconjunctivitis being reported by the ophthalmology team led us to investigate if these were due to a specific AdV species. Initial typing was performed by sending AdV positive samples to a commercial laboratory (Micropathology Ltd.), with further confirmatory typing and additional genotyping by partial hexon gene sequencing at the PHE Reference Laboratory (PHE National Infection Service). In total, 49 of the 126 AdV positive samples obtained during the March–August 2019 period were sequenced, of which two failed due to low viral load (Table S1).

Of those successfully sequenced, 15 samples were typed only to species D level. However, from the viral sequencing results, all the species D viruses that could be typed were typed as AdV D8, so it is reasonable to assume that these 15 untyped species D viruses were also genotyped D8 (Table 1, Figure 2). Nevertheless, for the purposes

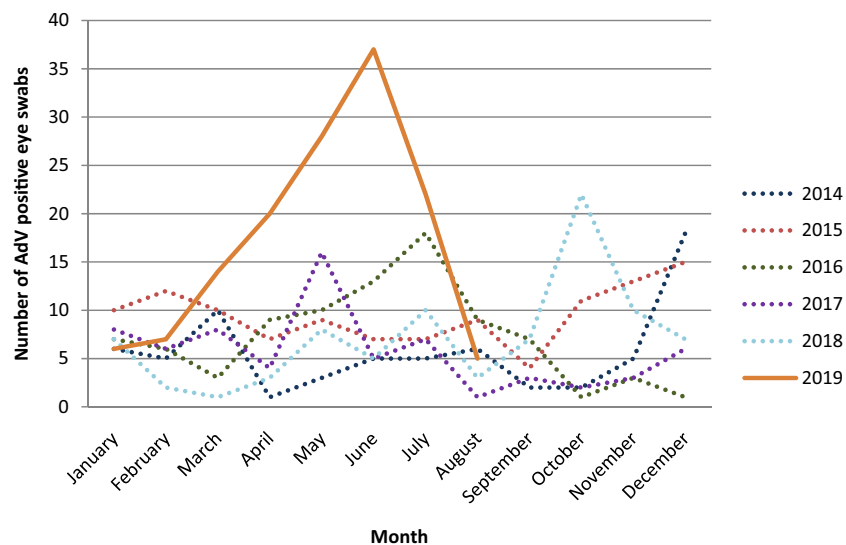
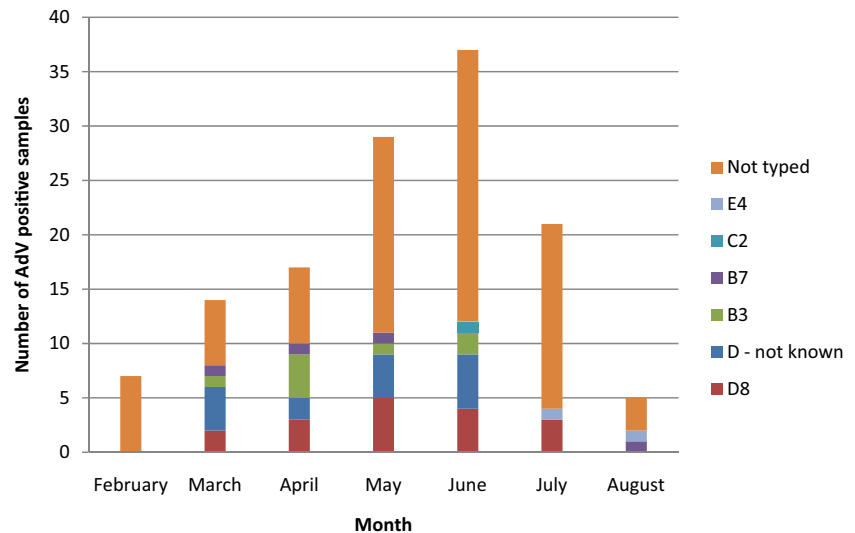


FIGURE 1 Confirmed cases of adenovirus (AdV) conjunctivitis 2014–2019, Leicester UK. Note that the small peak of infections towards the end of 2018 is unlikely to be linked to the current outbreak, as the number of cases returns to baseline during December 2018 and January 2019

FIGURE 2 Total number of adenovirus (AdV) positive eye swabs per month by typing in 2019 cases



of comparison to the other AdV types detected, we only used the data that were certain, that is, to species D only. A χ^2 test was used to demonstrate that the number of typed cases attributable to species D was statistically significant over nonspecies D cases ($p < .025$), thus rejecting the null hypothesis that there were no one particular species behind the outbreak. Other nonspecies D AdV types included B3, B7, C4, and E2.

Among the AdV species D cases, we observed that 66% of outbreak patients had bilateral disease but 52% of them only suffered

from conjunctivitis rather than keratitis (34%). It is clear that though rates of keratitis seen were much higher in the D group (34%) compared to other AdV types, rates of PF and SPK were not necessarily higher in the outbreak group (14% and 10%, respectively) compared to those with subgenus B AdV infection (27% and 17%, respectively). Only one patient for whom typing data was available (AdV D) had PEE. Furthermore, a statistical comparison also demonstrated that the disease severity did not vary significantly between the AdV D and non-D (B, C, and E) species (Table 1). With

TABLE 1 Demographics and disease severity by adenovirus (AdV) type

AdV type	B n = 12	C n = 1	E n = 1	B, C, and E n = 14	D n = 31	Total n = 48
Age	37 (18–57)	62	41	39 (27– 58)	48 (33–69)	41 (29–63)
Sex—Female	9 (75%)	1 (100%)	0 (0%)	10 (71%)	19 (61%)	31 (65%)
Complicated	5 (42%)	0 (0%)	1 (100%)	6 (43%)	16 (52%)	24 (50%)
Bilateral						
Both	7 (58%)	0 (0%)	0 (0%)	7 (50%)	19 (66%)	28 (61%)
Left	3 (25%)	0 (0%)	0 (0%)	3 (21%)	3 (10%)	7 (15%)
Right	2 (17%)	1 (100%)	1 (100%)	4 (29%)	7 (24%)	11 (24%)
Cornea						
Keratitis	1 (8%)	0 (0%)	0 (0%)	1 (7%)	10 (34%)	13 (28%)
PEE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	1 (2%)
SPK	2 (17%)	0 (0%)	0 (0%)	2 (14%)	3 (10%)	5 (11%)
Clear	9 (75%)	1 (100%)	1 (100%)	11 (79%)	15 (52%)	27 (59%)
Pseudomembrane						
Yes	3 (27%)	0 (0%)	1 (100%)	4 (31%)	4 (14%)	8 (18%)
No	8 (73%)	1 (100%)	0 (0%)	9 (69%)	24 (86%)	36 (82%)

Note: Complicated defined as either cornea involvement with keratitis/PEE/SPK or pseudomembrane formation.

Three patients with missing Adv type.

Abbreviations: PEE, punctate epithelial erosions; SPK, superficial punctate keratitis.

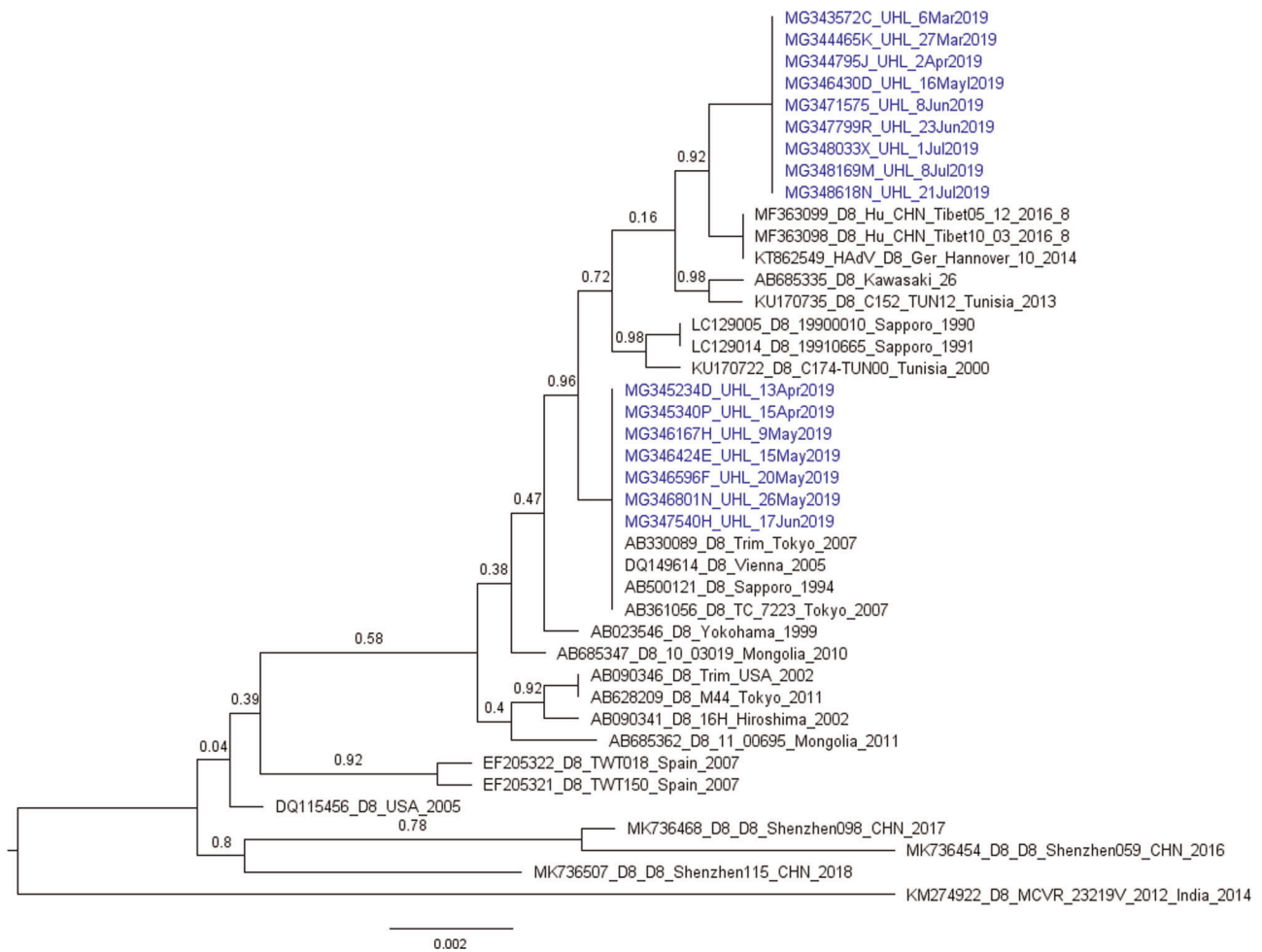


FIGURE 3 Maximum-likelihood tree using hexon partial gene sequences of 993 bp. The Leicester adenovirus D8 sequences (blue font) are most closely related to either virus sequences from outbreaks of epidemic keratoconjunctivitis in Germany/Tibet or from Japan/Europe

the small differences observed, further statistical analysis was not likely to allow us to draw any additional conclusions.

A phylogenetic analysis of the AdV hexon gene sequences was also performed. A maximum-likelihood tree was constructed using Fast Tree (v2.1) under a generalised time-reversible model of evolution, using hexon partial gene sequences of 993 bp, aligned in BioEdit (v7.2) and displayed in FigTree v1.4.4. This analysis showed two distinct outbreak lineages. One lineage clustered separately and showed the greatest similarity to an AdV D8 identified during outbreaks of EK in Germany in 2012–2013 and Tibet in 2016; and the second cluster was identical to older AdV D8 sequences from Japan and Europe. This may indicate two separate sources; however, no additional background contact information was obtained on this possibility during the routine clerking of these patients (Figure 3).

4 | DISCUSSION

This outbreak of AdV D8 EK in this Leicester UK population was unexpected and large, with two apparent AdV D8 lineages (Figure 3), and caused significant morbidity in both patients and some

healthcare staff. The outbreak ultimately proved to be self-limiting with a return in the incidence of cases to numbers seen in previous years with no point sources for either AdV D8 lineage identified. Contact tracing of cases was not undertaken though.

In addition, during the outbreak, five staff (including doctors, nurses, and healthcare assistants) in the ophthalmology department contracted AdV keratoconjunctivitis. These infected staffs were identified purely on clinical grounds and were not swabbed and tested for AdV. They may have contracted the AdV from their infected patients or could have been just another case of the community outbreak that was ongoing, involving these patients. The former would have demonstrated a significant failure of infection control at some stage during the patient's assessment and management, though this transmission route cannot be confirmed without the viral sampling and sequencing analysis of the virus from these staff. It has been shown previously that alcohol gel hand rubs are an inadequate cleansing method for AdV.⁴ If these were hospital-acquired infections, then it is possible that improved handwashing (rather than the use of alcohol gels), fomite, and equipment cleaning could have prevented some of these cases.¹⁴

Though the more clinically severe disease was seen, the ophthalmology team were of the opinion that this was likely just a reflection of the increased overall number of AdV EK cases rather than the AdV species D viruses causing more severe disease than the other circulating AdV species. This is supported by the results in Table 1, which showed that there were no statistical differences in the severity of clinical disease between the different AdV species. While this means we could not reject our null hypothesis, the small sample size means further data would be needed to determine which AdV types cause more severe eye disease. Beyond the increased burden of EK, we did not find higher rates of PF or SPK compared with the nonepidemic (i.e., non-AdV D) circulating strains. In our outbreak, we observed lower rates of PF than described in previous outbreaks with AdV D8,¹⁰ though differences in clinical severity within AdV species have been observed previously.^{15,16}

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Julian W. Tang and Joyce Burns conceived of the presented study. Oliver T. R. Toovey, Priti Kulkarni, Joicy David, Ayushi Patel, Catherine Thompson, and Joanna Ellis were involved in data collection. Oliver T. R. Toovey, Florence Y. Lai, Catherine Thompson, and Joanna Ellis were involved in data analysis and interpretation. Oliver T. R. Toovey and Priti Kulkarni drafted the article. All authors were involved in critical appraisal of the article and gave final approval of the version to be published.

DATA AVAILABILITY STATEMENT

The original data are available from the authors upon request –with reasonable justification.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Toovey OTR, Kulkarni P, David J, et al. An outbreak of adenovirus D8 keratoconjunctivitis in Leicester, United Kingdom, from March to August 2019. *J Med Virol.* 2021; 93:3969–3973. <https://doi.org/10.1002/jmv.26647>