Epidemiol. Infect. (1994), **112**, 463–471

An epidemic of cholera due to *Vibrio cholerae* O139 in Dhaka, Bangladesh: clinical and epidemiological features

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(*Accepted 4 January 1994*)

SUMMARY

We describe the disease spectrum and socio-demographic and epidemiological features of an epidemic of cholera due to a new pathogen, *Vibrio cholerae* O139, in patients attending a very large hospital in the metropolitan city of Dhaka, Bangladesh.

This hospital treats 70000–90000 patients a year with diarrhoeal diseases. A 4% systematic sample of 1854 patients attending from January to April 1993 were studied.

Five hundred and two (27%) of the 1854 patients were culture positive for *V. cholerae* O139 and 63 (3%) were culture positive for *V. cholerae* O1 biotype El Tor. Patients with *V. cholerae* O139 were mainly adults with a short history of watery diarrhoea. Eight-three percent of patients had moderate to severe dehydration. All recovered except one 80-year-old man with compromised renal function who died. Seventy-eight percent of patients required initial intravenous rehydration followed by oral rehydration therapy with rice ORS; they also received tetracycline to reduce diarrhoea severity. Most patients were from urban slums with inadequate sanitation facilities and hygiene practices.

The newly recognized *V. cholerae* O139 infection produced an epidemic of severe dehydrating diarrhoea indistinguishable from clinical cholera in a population which experiences two epidemic peaks of cholera in a year due to *V. cholerae* O1. Infection with the latter does not appear to confer any cross-protection from *V. cholerae* O139. The new pathogen suppressed, albeit temporarily, *V. cholerae* O1. Unlike other non-O1 serogroups of *V. cholerae* this new serogroup appears to have epidemic potential.

INTRODUCTION

Recently large epidemics of diarrhoea have been reported from India [1] and Bangladesh [2] caused by *Vibrio cholerae* that do not agglutinate with O1 antiserum or with any of the 137 known non-O1 serogroups and has been designated *V. cholerae* O139 synonym Bengal [3]. Hitherto, only strains of O1 serogroup were known to cause cholera and to have epidemic and pandemic potential; non-O1 *V. cholerae* are widely distributed in water and are known to

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cause sporadic diarrhoea and occasionally extraintestinal infections [4]. This new serogroup, *V. cholerae* O139, was shown to consistently produce cholera toxin indistinguishable from the toxin of *V. cholerae* O1: it was also shown to possess virulence properties in animal models [1–3]. Unofficial reports indicate that several more outbreaks of this disease have already occurred in various parts of India and Bangladesh, and recently cases have been reported from Thailand, Nepal, China, Pakistan and Malaysia.

Between the middle of January and April 1993, *V. cholerae* O139 was associated with a large epidemic of cholera-like disease in the metropolitan city of Dhaka. The treatment facility of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B) located in Dhaka provides free treatment to patients with diarrhoeal disease of all severity, and on average 200–300 patients attend every day; in a year 70–90000 patients with diarrhoeal diseases are treated. Other hospitals in the city do not admit patients with diarrhoea. Because of the above and the Centre's reputation built over 30 years, an overwhelming majority of patients with diarrhoea in the greater Dhaka city area attend this hospital. Since 1981, the facility has maintained a surveillance system to monitor the characteristics of the patient population and aetiologic agents [5]. In this programme, data are collected from a 4% systematic sample of all patients attending the facility. This hospital based surveillance system was in place when the epidemic caused by *V. cholerae* O139 occurred in Dhaka and offered a unique opportunity to study this new epidemic. We describe the disease, socio-demographic features of the patients, and some epidemiologic features.

METHODS

In the surveillance programme every twenty-fifth patient is interviewed by experienced health workers who administer a detailed questionnaire recording demographic and socioeconomic characteristics, hygiene practices, and medical history, and is also examined by a physician. Stool specimens are obtained for microscopic examination and culture. Information on therapy received and on the course of illness is recorded. Data from precoded questionnaires are entered into a microcomputer as they are collected.

Five hundred and two patients whose faeces were positive for *V. cholerae* O139 up to April out of 1854 surveillance patients, were compared with patients negative for *V. cholerae* O139. Because this new epidemic occurred in a city where cholera due to *V. cholerae* O1 occurs regularly with two yearly peaks, we have also summarized the cholera situation in the city over the last 10 years using the computerized data base of this surveillance system. SPSS PC+ software was used to analyse the data.

Standard microbiological methods as described previously [6] were used. They included TTGA (taurocholate-tellurite-gelatin agar) for isolation of vibrios (7). The *V. cholerae* non-O1 strains were tested against antisera raised against *V. cholerae* O139 in our research laboratories for confirmation.

RESULTS

In 1993, the weekly attendance of patients at this hospital started to increase from the third week of January (Fig. 1*a*). This followed a very large annual

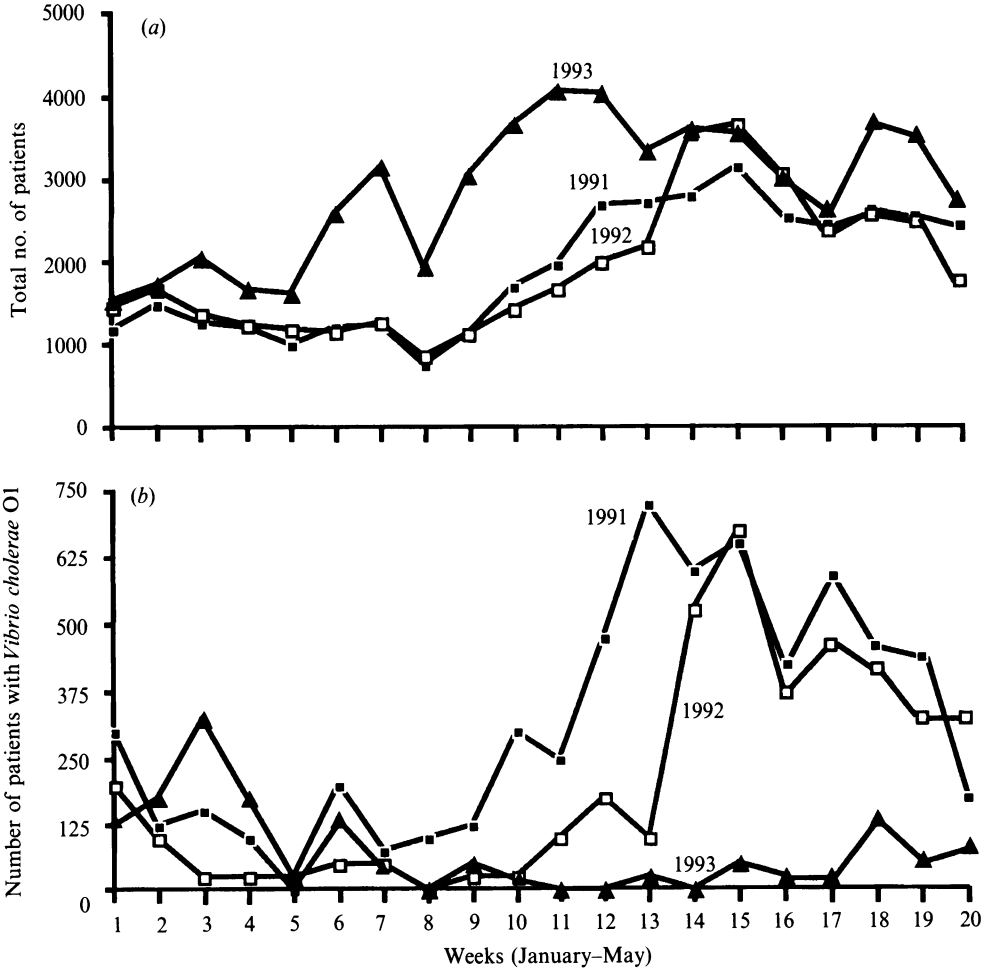

Fig. 1. (*a*) Weekly total number of patients attending the Dhaka Diarrhoea Hospital, January–April 1991, 1992 and 1993. (*b*) Weekly number of patients with *Vibrio cholerae* O1 estimated from culture proven cases among a 4% systematic sample of all patients attending the Dhaka Diarrhoea Hospital, January–April 1991, 1992 and 1993.

religious meeting near Dhaka, along the river Turag, from 16-18 January 1993, with an estimated 2 million pilgrims mostly from Bangladesh, and the rest from about 60 different countries. In the peak months of February and March, twice as many patients were seen compared with previous years (Fig. 1*a*). In 1991 and 1992 the number of patients attending started to increase from week 8 and this was accounted for by patients with *V. cholerae* O1. In 1993 numbers of cases of *V. cholerae* O1 remained very low (Figs. 1*b*, 2). The sustained level of attendance during April and May 1993 (Fig. 1*a*) was largely accounted for by *V. cholerae* O139 (Fig. 2). The proportion of patients with *V. cholerae* O139 was as high as 34% and above from the 6th week till the 12th week (43%), and by the 20th week the proportion still remained high at 10%.

The age and sex distribution of 502 diarrhoeal patients in the surveillance system with *V. cholerae* O139 were compared with 63 patients with *V. cholerae* O1 and 1289 patients with diarrhoea due to other causes (Table 1). Seventy one percent of patients with *V. cholerae* O139 were adults ($\geqslant$ 15 years of age)

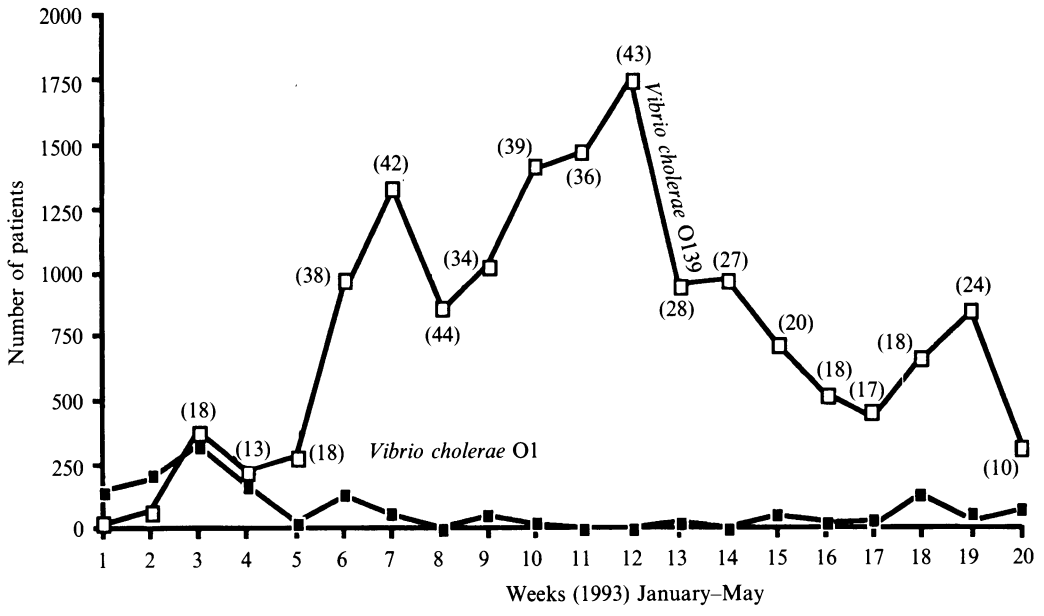

Fig. 2. Weekly number of patients with *Vibrio cholerae* O139 and *Vibrio cholerae* O1 estimated from culture proven cases among a 4% systematic sample of patients attending the Dhaka diarrhoea hospital. Numbers in parenthesis are percentages of patients examined.

Table 1. *Numbers (percentages) of patients by age and sex (4% systematic sample) with* Vibrio cholerae *O139,* Vibrio cholerae *O1 and other causes attending the diarrhoea treatment centre, Dhaka, January–April 1993*

Age (years)	*Vibrio cholerae* O139			*Vibrio cholerae* O1			Others		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
0–4	50	35	85	17	4	21	460	289	749
	(17·3)	(16·5)	(16·9)	(40·4)	(19·0)	(33·3)	(58·7)	(57·1)	(58·1)
5–9	20	19	39	5	2	7	34	30	64
	(6·9)	(9·0)	(7·8)	(11·9)	(9·5)	(11·1)	(4·3)	(5·9)	(5·0)
10–14	8	13	21	2	3	5	25	20	45
	(2·8)	(6·1)	(4·2)	(4·8)	(14·3)	(7·9)	(3·2)	(4·0)	(3·5)
15–49	126	113	239	12	7	19	200	133	333
	(43·4)	(53·3)	(47·6)	(28·6)	(33·3)	(30·2)	(25·5)	(26·3)	(25·8)
50+	86	32	118	6	5	11	64	34	98
	(29·7)	(15·1)	(23·5)	(14·3)	(23·8)	(17·5)	(8·2)	(6·7)	(7·6)
Total	290	212	502	42	21	63	783	506	1289

compared to 48% of patients with *V. cholerae* O1 and 33% of patients with other causes. Duration of diarrhoea and vomiting prior to attending the treatment centre (median duration 14 h) was shorter in patients with O139, but stool frequency was similar to O1 patients. A higher proportion of O139 patients (44%) complained of abdominal pain or cramps (Table 2). They were generally afebrile but more than 80% had moderate to severe dehydration.

Socioeconomic status and water and sanitation practices of patients with *V. cholerae* O139 were generally poor (Table 3); the median per capita income was about 50% of the national average. This hospital treats patients mainly from the

Table 2. *Clinical features (percentages) of diarrhoea patients positive for* Vibrio cholerae *O139 compared to those with* Vibrio cholerae *O1 and other causes of diarrhoea attending the diarrhoea treatment centre in Dhaka, Bangladesh, January–April 1993*

Patient characteristics	*Vibrio cholerae* O139 ($n = 502$)	*Vibrio cholerae* O1 ($n = 63$)	Other causes ($n = 1289$)
Replacement fluid at home			
None	13·0	14·3	16·8
Packet ORS	71·9	65·1	73·8
Home made ORS	6·6	9·5	5·4
I.V. fluid with or without ORS	8·6	11·1	4·0
Anti-microbials at home	45·4	54·0	56·6
Median duration of diarrhoea in hours (quartiles)	14 (8–28)	17 (7–50)	37 (15–96)
Stool frequency in last 24 h before admission			
3–5	9·0	9·5	15·1
6–10	40·8	39·7	42·1
> 11	50·2	50·8	42·8
Watery stools reported on admission	97·4	98·4	86·3
Abdominal pain/cramp on admission	43·8	30·2	36·0
Fever on admission (> 37·7 °C)	1·2	0·0	7·9
Rehydration on admission			
None	1·4	6·3	5·6
Mild	15·5	12·7	56·6
Moderate	31·1	31·7	24·9
Severe	52·0	49·2	13·0
Rehydration method in hospital			
None	0·0	0·0	0·9
Only ORS	22·6	28·6	71·7
I.V. + ORS	77·5	71·5	27·4
Median duration of hospital stay, hours (quartiles)	18·0 (8·0–26·0)	21·0 (16·0–39·0)	9·0 (3·0–22·0)

Table 3. *Socioeconomic status and water and sanitation practices of patients with* Vibrio cholerae *O139*, Vibrio cholerae *O1 and other diarrhoeal diseases attending the diarrhoea treatment centre in Dhaka, Bangladesh, January–April 1993*

	Vibrio cholerae O139 ($n = 502$)	*Vibrio cholerae* O1 ($n = 63$)	Other causes ($n = 1289$)
In house drinking water present (%)	7·2	1·6	10·2
Type of latrine			
Sanitary or semi-sanitary	30·7	19·1	40·6
Dug hole or open pit	49·2	55·5	46·4
Hanging or service	19·1	22·2	11·8
No fixed place	1·0	3·2	1·2
Median monthly family income in Taka*	2150 (1500–3050)	2500 (1700–3500)	2500 (1600–4000)
House floor (%)			
Not cemented	60·6	76·6	53·6
Cemented	39·4	23·4	46·4

* 1 pound = Taka 60 (approximately).

Table 4. *Clinical features in children under 5 years compared to those 15 years and above with diarrhoea due to* Vibrio cholerae *O139 attending the diarrhoea treatment centre, Dhaka, Bangladesh, January–April 1993*

Characteristics	0–4 years ($n = 85$)	⩾ 15 years ($n = 357$)
Duration of diarrhoea before coming to hospital (%)		
0–12 h	27·1	48·2
12–24 h	12·9	27·2
> 24 h	60·0	24·6
Stool frequency in 24 h before admission (%)		
3–5	12·9	7·3
6–10	43·5	39·2
11+	43·6	53·5
Frequency of vomiting 24 h before admission		
None	11·8	13·4
1–9	70·6	74·2
10+	17·6	12·3
Dehydration on admission		
None	2·4	1·4
Mild	34·1	12·6
Moderate	44·7	27·2
Severe	18·8	58·8
Rehydration fluids used at hospital		
Only ORS	47·0	16·9
I.V. + ORS	53·2	83·1
Duration of stay in hospital		
0–11 h	27·4	41·2
12–23 h	26·2	36·1
24–35 h	14·3	12·2
⩾ 36 h	32·1	10·5

urban poor and the patient population with *V. cholerae* O139 was similar to the patient population with other causes of diarrhoea.

The disease was generally milder in children under 5 years compared to older patients and nearly half of them could be maintained with oral rehydration therapy alone compared to only 17% of older patients (Table 4). However, the hospital stay was somewhat longer for children which may largely reflect policy and the logistic constraints of sending them home.

This epidemic occurred in a city where cholera occurs regularly with two peaks due to *V. cholerae* O1. In view of its relevance to immunity against the new *V. cholerae* O139, we summarize cholera incidence for the last 10 years (Table 5) and the incidence of all common bacterial pathogens for diarrhoea for the previous year 1992 (Table 6). The proportion of patients with cholera (due to *V. cholerae* O1) varied from 4·4–20·3% a year (Table 5). Large epidemics occurred in 1986–8 but the proportion fell in 1989–90 to rise again during 1991–2. The proportion of cholera cases with *V. cholerae* O1 classical biotype was high in 1983 but decreased

Table 5. Vibrio cholerae *O1 detected among surveillance patients (4% systematic sample) at the diarrhoea treatment centre over 10 years (1983–92)*

Year	No. screened	*V. cholerae* O1 (%)			Estimated total of cholera patients
		Classical	El Tor	Total	
1983	2854	117 (4·1)	253 (8·8)	370 (13·0)	9250
1984	2945	34 (1·2)	308 (10·5)	342 (11·6)	8550
1985	2287	40 (1·7)	215 (9·4)	255 (11·1)	6375
1986	2580	259 (10·0)	251 (9·7)	510 (19·8)	12750
1987	2789	272 (9·8)	295 (10·6)	567 (20·3)	14175
1988	3262	68 (2·1)	482 (14·8)	550 (16·9)	13750
1989	2384	10 (0·4)	94 (3·9)	104 (4·4)	2600
1990	2383	2 (0·1)	141 (5·9)	143 (6·0)	3575
1991	3641	7 (0·2)	658 (18·1)	665 (18·3)	16625
1992	3474	2 (0·1)	516 (14·9)	518 (14·9)	12950
Total	28599	811 (2·8)	3213 (11·2)	4024 (14·0)	100600

Table 6. Vibrio cholerae *O1 and other bacterial pathogens detected in surveillance patients in 1992 (4% systematic sample of all diarrhoea cases attending)*

Months	No. surveyed	*Vibrio cholerae* O1	*Vibrio cholerae* non-O1	Other vibrios*	*Campylobacter jejuni*	*Shigella*† species	*Salmonella*‡ species
Jan	230	14	0	23	ND	33	3
Feb	180	5	0	22	ND	22	4
March	249	13	0	60	ND	21	4
April	498	67	1	77	ND	48	6
May	364	61	3	40	ND	48	4
June	243	42	2	38	22	37	14
July	240	26	3	42	44	18	10
Aug	289	50	1	31	57	33	13
Sept	263	51	1	57	44	22	13
Oct	307	71	5	58	35	32	20
Nov	334	74	2	48	33	24	14
Dec	317	44	1	50	39	40	7
Total	3514	518	19	546	274	378	112
(%)	(4%)	(14·7%)	(0·54%)	(15·5%)	(13·7%)	(10·8%)	(3·2%)
Estimated total	87850	12950	475	13650	—	9450	2800

* Includes *Aeromonas hydrophila* and *Plesiomonas shigelloides*.
† Predominantly *Shigella flexneri* and *Shigella dysenteriae* 1.
‡ Includes typhoid and non-typhoid salmonellae.
ND, not done.

to only 10–15% of positive cases in 1984–5 to rise again to about 50% of cases in 1986–7, after which it became rare. During these years the isolation of *V. cholerae* non-O1 was sporadic and similar to that shown for 1992 (Table 6); the two usual epidemic peaks for cholera due to *V. cholerae* O1, i.e. April/May and October/November, were also apparent (Table 6).

DISCUSSION

Earlier studies have reported sporadic cases of diarrhoea due to *V. cholerae* non-O1 in Asia, Africa, Europe, and North and South America. In Dhaka, *V. cholerae* non-O1 were isolated from 3% (34 out of 1120) of hospitalized diarrhoeal cases

and from less than 0·1 % (1 out of 6951) of healthy persons during the early 1960s [8]. In 1979, Spira and colleagues [9] described the characteristics of 14 diarrhoeal cases attending the diarrhoea hospital of ICDDR, B in Dhaka from whom *V. cholerae* non-O1 was found to be the only potential diarrhoeal pathogen. Between 1970 and 1977, the treatment facility at ICDDR, B admitted about 475 cases of diarrhoea associated with isolation of *V. cholerae* non-O1. During these years, the seasonality of *V. cholerae* non-O1 cases was similar to that of *V. cholerae* O1; the number of sporadic cases increased in March–April and in October–November [10]. A few small outbreaks of diarrhoeal illnesses associated with *V. cholerae* non-O1 infection have been reported in Czechoslovakia [11], Sudan [12], Australia [13] and the United States [14]. However, epidemics of cholera-like disease due to *V. cholerae* non-O1 have not been reported until the present epidemic.

We have described an epidemic of severe cholera-like diarrhoea predominantly in adults affecting the greater part of the metropolitan city of Dhaka, Bangladesh associated with a new serogroup of *V. cholerae* now named as *V. cholerae* O139. All 502 recovered except one 80-year-old man who was admitted with diarrhoea and vomiting for less than 24 h and died within 24 h of treatment. Only scanty medical history was available and he had evidence of impaired renal function, as indicated by high serum creatinine level (368 μmol/litre) after rehydration.

As with cholera, the clinical spectrum of the disease ranged from very mild diarrhoea, requiring no treatment, to severe dehydrating diarrhoea. However, most cases were adults with severe disease indistinguishable from clinical cholera. This is consistent with the introduction of a new pathogen into a virgin population. The patients came from the same poor urban area with poor sanitation and water use practices who are more likely to be exposed to the new epidemic strain of *V. cholerae*. Patients who were infants and children had a milder disease. Unlike *V. cholerae* O1 of recent months in Dhaka, this organism was susceptible to tetracycline, ampicillin, chloramphenicol, erythromycin and ciprofloxacin but was resistant to cotrimoxazole. Patients received tetracycline routinely. However, studies are needed to confirm that, as in cholera, use of a suitable antibiotic will also reduce the severity and duration of diarrhoea due to *V. cholerae* O139.

This untimely epidemic of severe life-threatening diarrhoea appeared to have started from the time of a very large religious congregation. A likely scenario in Bangladesh may have been that the outbreak initially started in the southern districts of Bangladesh (coastal districts). The very large congregation helped its spread in the metropolitan city of Dhaka and in other districts of Bangladesh through returning pilgrims.

Further studies are needed on the nature of this organism, its implications for the development of vaccines against cholera and cholera-like disease, the nature of its spread in the community and evaluation of case management with particular reference to the role of antibiotics and oral rehydration therapy.

ACKNOWLEDGEMENTS

This research was supported by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B). The ICDDR, B is supported by countries and agencies which share its concern for the health problems of developing countries.

Current donors include: the aid agencies of the Governments of Australia, Bangladesh, Belgium, Canada, Denmark, France, Japan, the Netherlands, Norway, Saudi Arabia, Sweden, Switzerland, the United Kingdom and the United States; international organizations including the United Nations Children's Fund, the United Nations Development Programme, the United Nations Population Fund (UNFPA), and the World Health Organization; and private foundations including the Ford Foundation and the Sasakawa Foundation.

We would like to thank Professor J. R. Hamilton, McGill University, Montreal, Canada for critically reviewing the manuscript and to Ms Loretta Saldanha-Ansari for typing and editing the same.

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