

!" #&/
4;O <548G=>3> 70AB>AC20==O ;V:0@AL:>3> 70A>1C

&□\$□ !
(CEFAXONE)

!,:04:

4VNG0 @5G>28=0: Aeftriaxone;
1 D;0:>= =C =0B@VN C ?5@5@0EC20==V =0 F5DB@80:A>= 1 3.

V:0@AL:0 D>@<0. >@>H>: 4;O @>7G8=C 4;O V=T: FV9.
A=>2=V DV78:>-EVABV: :@8AB0;VG=89 ?>@>H>: 2V4 1V;>3> 4> 6>2BC20B>->@0=652>3> :>;L>@C.

\$0@<0:>B5@0?52B8G=0 3@C?0. =B810:B5@V0;L=V 70A>18 4;O A8AB5<=>3> 70AB>AC20==O. =HV
β-;0:B0<=V 0=B81V>B8:8. ?>A?>@8=8 III ?>:>;V==O. &5DB@80:A>=. >4 "% J01D D04.

\$0@<0:>;>3VG=V 2;0AB82>ABV.

\$0@<0:>48=0
&5DB@80:A>= ?0@5=B5@0;L=89 F5D0;>A?>@8=>289 0=B81V>B8: III ?>:>;V==O 7 ?@>;>=3>20=>N 4VTN.
5E0=V7< 4VW.

0:B5@8F84=0 0:B82=VABL F5DB@80:A>=C 7C<>2;5=0 ?@83=VG5==O< A8=B57C ;;VB8==>W ABV=:8. &5DB@80:A>= 0:B82=89 *in vitro* 2V4=>A=>
H8@>:>3> A?5:B@C 3@0<=530B82=8E V 3@078B82=8E >@30=V7= E0@0:B5@87CTBLAO 4C65 25;8:>N ABV9:VABN 4> 1V;LH>ABV□-;0:B0<07 (O:
?5=VF8;V=07, B0: V F5D0;>A?>@8=07) 3@078B82=8E V 3@0<=530B82=8E 10:B5@V9. &5DB@80:A>= 728G09=> 0:B82=89 2V4=>A=> B0:8E >@30=V7
in vitro B0 ?@8 ;;V=VG=8E V=D5:FVOE:

3@078B82=V 05@>18: Staphylococcus aureus(<5B8F8;V=>GCB;8289), :>03C;07>=530B82=V AB0DV;>:>:8, *Streptococcus pyogenes* (β-35<>;VB8G=89,
3@C?8), *Streptococcus agalactiae*

(β-35<>;VB8G=89, 3@C?8), β-35<>;VB8G=V AB@5?B>:>:8 (3@C?8 =V , =V), *Streptococcus viridans*, *Streptococcus pneumoniae*.

@8 !BV9:V 4> <5B8F8;V=C *Staphylococcus spp.* @578AB5=B=V 4> F5D0;>A?>@8=V2, C B> F5DB@80:A>=C. "0:>6 *Enterococcus faecalis*, *Enterococcus faecium* B0 *Listeria monocytogenes*?@>O2;ONBL ABV9:VABL4> F5DB@80:A>=C.

@0<=530B82=V 05@>18: Acinetobacter lwoffii, *Acinetobacter anitratus*(3>;>2=8< G8=>< *A. baumannii*)*, *Aeromonas hydrophila*, *Alcaligenes faecalis*, *Alcaligenes odorans*, 0;:035=>?>4V1=V 10:B5@VW, *Borrelia burgdorferi*, *Burkholderia cepacia*, *Capnocytophaga spp.*, *Citrobacter diversus* (C B> G8A;V
C. amalonaticus), *Citrobacter freundii**, *Escherichia coli*, *Enterobacter aerogenes**, *Enterobacter cloacae**, *Enterobacter spp.* (V=HV)*, *Haemophilus ducreyi*,
Haemophilus influenzae, *Haemophilus parainfluenzae*, *Hafnia alvei*, *Klebsiella oxytoca*, *Klebsiella pneumoniae***, *Moraxella catarrhalis*(@0=VH5 =07820;8AO
Branhamella catarrhalis), *Moraxella osloensis*, *Moraxella spp.* (V=HV), *Morganella morganii*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pasteurella multocida*,
Plesiomonas shigelloides, *Proteus mirabilis*, *Proteus pennneri**, *Proteus vulgaris*, *Pseudomonas fluorescens**, *Pseudomonas spp.* (V=HV)*, *Providentia rettgeri*,
Providentia spp. (V=HV), *Salmonella typhi*, *Salmonella spp.* (3@C?0 enteritidis), *Serratia marcescens*, *Serratia spp.* (V=HV), *Shigella spp.*, *Vibrio spp.*, *Yersinia enterocolitica*, *Yersinia spp.* (V=HV).

* 45O:V V7>;OB8 F8E 284V2 ABV9:V 4> F5DB@80:A>=C 3>;>2=8< G8=>< C=0A;V4>: CB2>@5==O β-;0:B0<07, I> :>4CNBLAO E@><>A><0<8.

** 45O:V V7>;OB8 *Klebsiella pneumoniae* ABV9:V 4> F5DB@80:A>=C C=0A;V4>: CB2>@5==O =87:8 ?;07->?>A5@54:>20=8E β-;0:B0<07.
@8 030B> 7 HB0>@30=V7 4> B0:8E 0=B81V>B8:V2 O: 0?5=VF8;V=8 B0 C@5W4>?5=VF8;V=8, F5D0;>A?>@8=8 B0 ?>:>;V==O, 03;V:>7848, T GCB;828
<8 4> F5DB@80:A>=C. *Treponema pallidum* GCB;820 4> F5DB@80:A>=C *in vitro* B0 2 4>A;V40E =0 B20@8=0E. ;V=VG=V 28?@>1C20==O ?>:07CNBL, I>
F5DB@80:A>= 5D5:B82=89 4;O ;V:C20==O ?5@28==>3> B0 2B>@8==>3> A8DV;VAC. 0 45O:8<8 28=OB:0<8 ;;V=VG=V HB0<8
P. 0eruginosa ABV9:V 4> F5DB@80:A>=C.

=05@>18: *Bacteroides* spp. (GCB;82V 4> 6>2GV)*, *Clostridium* spp. (:@V< 3@C?8 *C. perfringens*), *Fusobacterium nucleatum*, *Fusobacterium* spp. (V=HV),
Gaffkia anaerobica(@0=VH5 =07820;8AO *Peptococcus*), *Peptostreptococci*.

* 45O:V V7>;OB8 *Bacteroides* spp. ABV9:V 4> F5DB@80:A>=C.
@8 030B> 7 HB0 *Bacteroides* spp., O:V ?@>4C:CNBL □-;0:B0<078 (7>:@5<0, *B. fragilis*), ABV9:V 4> F5DB@80:A>=C. !BV9:89 *Clostridium difficile*.
'CB;82VABL 4> F5DB@80:A>=C<>6=0 287=0G0B8 <5B>4>< 48A:V2 01> <5B>4>< A5@V9=8E @>72545=L =0 030@V 01> 1C;L9>=V, 28:>@8AB>2CNG8
AB0=40@B=C <5B>48:C, ?>4V1=C 4> BVTW, O:C @5:>5=4CT 0FV>=0;L=89 :>@0B>@=8E AB0=40@BV2 (!). ;O F5DB@80:A>=C ! 2AB0=>282 B0:V
:@8B5@VW >FV=:8 @57C;LB0BV2 28?@>1C20=L:

	CB;82V	>GCB;82V	!BV9:V
5B>4 @>72545=L =3V1CNG0 :>=F5=B@0FVO, <3/; ≤ 8		16-32	≥ 64
5B>4 48A:V2 (48A: 7 30 =C) V0<5B@ 7>=8 70B@8ABC, <<	≥ 21	20-14	≤ 13

;O 287=0G5==O GCB;82>ABV >@30=V7@8AB>2C20B8 48A:8 7 F5DB@80:A>=><, B0: O: C 4>A;V465==OE *in vitro*?>:070=>, I> F5DB@80:A>= 0:B82=89
2V4=>A=> >:@5<8E HB0@8AB0==V 48A:V2, ?@87=0G5=8E 4;O 2AVTW 3@C?8 F5D0;>A?>@8=V2.

0ABV >@30=V7
\$0@<0:>:V=5B8:0.
\$0@<0:>:V=5B8:0 F5DB@80:A>=C <0T =5;V=V9=89 E0@0:B5@. AV >A=>2=V D0@<0:>:V=5B8G=V ?0@0<5B@8, I> 107CNBLAO =0 7030;L=8E
:>=F5=B@0FVOE ?@5?0@0BC (2V;L=89 B0 72O70=89 7 1V;;0<8 F5DB@80:A>=), 70 28=OB:>< ?5@V>4C =0?V2282545==O, 70;560BL 2V4 4>78.
A<>:BC20==O.

0:A8<0;L=0 :>=F5=B@0FVO C ?;072V ?VA;O 2=CB@VH=L<O7>2>3> 22545==O 1 3 ?@5?0@0BC AB0=>28BL 81 <3/; B0 4>AO30TBLAO 70 2-3 3>48=8
?VA;O 22545==O. 4=>@07>2V 2=CB@VH=L>25==V V=DC7VW 1 3 B0 2 3 ?@872>4OBL G5@57 30 E28;8= 4> :>=F5=B@0FV9 168,1±28,2 B0 256,9 ±16,8
<3/; 2V4?>2V4=>. ;>I0 ?V4 :@82>N «:>=F5=B@0FVO-G0A» C ?;072V ?VA;O 2=CB@VH=L>25==>3> 22545==O 4>@V2=NT B0:V9 ?VA;O 2=CB@VH=L>
<O7>2>3> 22545==O. &5 >7=0G0T, I> 1V>4>ABC?=VABL F5DB@80:A>=C ?VA;O 2=CB@VH=L<O7>2>3> 22545==O AB0=>28BL 100 %.

>7?>4V;.
1□T< @>7?>4V;C F5DB@80:A>=C AB0=>28BL 7-12 ;. VA;O 2=CB@VH=L>25==>3> 22545==O F5DB@80:A>= H284:> ?@>=8:0T 2 V=B5@AB8FV0;L=C
@V48=C, 45 10:B5@8F84=V :>=F5=B@0FVW I>4> GCB;828E >@30=V7BO3>< 24 3>48=.
VA;O 22545==O C 4>7V 1-2 3 F5DB@80:A>= 4>1@5 ?@>=8:0T C B:0=8=8 B0 @V48=8 >@30=V7BO3>< 1V;LH =V6 24 3>48=8 9>3> :>=F5=B@0FVW
=01030B> ?5@528ICNBL 2G>282V4=8E H;OE0E, ?5GV=FV, A5@54=L>2V9 =>A0, :VAB:0E, 0 B0:>6 A?8==>7:>2V9, ?;52@0;L=V9 B0 A8=>2V0;L=V9
@V48=0E, C A5:@5BV ?@>AB0B8).

&5DB@80:A>= 72>@>B=> 72O7CTBLAO 7 0;L1C<, ?@8G> :>=F5=B@0FVW, =0?@8:;04, 7=86CNG8AL 7 95 % ?@8 :>=F5=B@0FVW C ?;072V <5=H5 100 <3/; 4> 85 % ?@8 :>=F5=B@0FVW 300 <3/;. 024O:8 =86GV9 :>=F5=B@0FVW 0;L1C3> F5DB@80:A>=C 2 =V9 28I0, =V6 C ?;072V.

&5DB@80:A>= ?@>=8:0T G5@57 70?0;5=V <>7:>2V >1>;>=:8 C 4VB59, C B. G. =>2>=0@>465=8E.

0:A8<0;L=0 :>=F5=B@0FVO C A?8==><>7:>2V9 @V48=V 4>AO30TBLAO ?@81;87=> G5@57 4 3>48=8 ?VA;O 2=CB@VH=L>25==>3> 22545==O B0 AB0=>28BL C A5@54=L>2V, ?@8 0A5?B8G=> 4>@>A;8E E2>@8E =0 <5=V=3VB ?VA;O 22545==O 4>78 50 <3/;3 G5@57 2-24 3>48=8 4>AO30NBLAO B0:V :>=F5=B@0FVW F5DB@80:A>=C C F5@51@>A?V=0;L=V9 @V48=V, O:V 2 1030B> @07V2 ?5@528ICNBL

&5DB@80:A>= ?@>E>48BL G5@57 ?;0F5=B0@=89 10@T@ B0 2 <0;8E :>=F5=B@0FVOE ?@>=8:0T C 3@C4=5 <>;>: (3-4 % 2V4 :>=F5=B@0FVW C ?;072V <0B5@V G5@57 4-6 3>48=).

5B01>;V7

&5DB@80:A>= =5 ?V440TBLAO A8AB5<=>@NTBLAO C =50:B82=V <5B01>;VB8 ?V4 4VTN :8H:>2>W D;>@8.

82545==O.

030;L=89 ?;07<>289 :;V@5=A F5DB@80:A>=C 4>@V2=NT 10-22 <;E2. 8@:>289 :;V@5=A 4>@V2=NT 5-12 <;E2. 50-60 % F5DB@80:A>=C 282>48BLAO C =572GN. 5@V>4 =0?V2282545==O F5DB@80:A>=C C 4>@>A;8E AB0=>28BL 1;87L:> 8 3>48=.

\$0@<0>:V=5B8:0 2 >A>I;828E ?>?C;OFVOE.

=>2>=0@>465=8E 4VB59 =8@:0<8 282>48BLAO ?@81;87=> 70 % 4>78. # 4VB59 ?5@H8E 8 4=V2 68BBO, 0 B0:>6 C ?0FVT=BV2 2V:< 2V4 75 @>:V2 ?5@V>4 =0?V2282545==O C A5@54=L>

E2>@8E V7 ;53:8< B0 ?>?>@CH5==O< DC=:FV9 =8@>: B0 ?5GV=:8 D0@<0>:V=5B8:0 F5DB@80:A>=C 7N N, 2V47=0G0TBLAO ;8H5 =57=0G=5 71V;LH5==O ?5@V>4C =0?V2282545==O 7 ?;07<8 :@>2V. /:I> ?>@CH5=0 ;8H5 DC=:FVO =8@>:, 71V;LHCTBLAO 282545==O 7 6>2GN, O:I> ?>@CH5=0 DC=:FVO ?5GV=:8, 71V;LHCTBLAO 282545==O =8@:0<8.

;V=VG=V E0@0:B5@8AB8:8.

>:070==O.

V:C20==O V=D5:FV9, 71C4=8:8 O:8E GCB;82V 4> F5DB@80:A>=C:

- V=D5:FVW 48E0;L=8E H;OEV2, >A>1;82> ?=52<>=VO, 0 B0:>6 V=D5:FVW 2CE0, 3>@;0 9 =>A0;
- V=D5:FVW >@30=V2 G5@52=>W ?>@>6=8=8 (?5@8B>=VB, V=D5:FVW 6>2G>282V4=8E H;OEV2 V B@02=>3> B@0:BC);
- V=D5:FVW =8@>: V A5G>282V4=8E H;OEV2;
- V=D5:FVW AB0B528E >@30=V2, 2;;NG0NG8 3>=>@5N;
- A5?A8A;
- V=D5:FVW :VAB>:, AC3;>1V2,<'O:8E B:0=8=, H:V@8, 0 B0:>6 @0=>2V V=D5:FVW;
- V=D5:FVW C E2>@8E 7 >A;01;5=8< V
- <5=V=3VB;
- 48A520=89 1>@5;V>7 09<0 (AB04VW B0);

5@V>?5@0FV9=0 ?@>DV;0:B8:0 V=D5:FV9 ?@8 EV@C@3VG=8E 2B@CG0==OE =0 >@30=0E B@02=>3> B@0:BC, 6>2G>282V4=8E H;OEV2, A5G>282V4=8E H;OEV2 V ?V4 G0A 3V=5:>;>3VG=8E ?@>F54C@, 0;5 ;8H5 C 28?04:0E ?>B5=FV9=>W G8 2V4><>W :>=B0 @8 ?@87=0G5==V &5D0:A>=C =5>1EV4=> 4>B@8DV9=8E @5:><5=40FV9 7 0=B81V>B8:>B5@0?VW B0, 7>:@5<0, @5:><5=40FV9 7 ?@>DV;0:B8:8 0=B81V>B8:>@578AB5=B=>ABV.

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> F5DB@80:A>=C 01> 1C4L-O:>3> V=H>3> F5D0;>A?>@8=C. 0O2=VABL 2 0=0=57V BO6:8E @50:FV9 3V?5@GCB;82>ABV
(=0?@8::04, 0=0DV;0:B8G=8E @50:FV9) 4> 1C4L-O:>3> V=H>3> B8?C β-;0:B0<=8E 0=B810:B5@V0;L=8E 70A>1V2 (?5=VF8;V=V2, <=>10:B0
&5DB@80:A>= ?@>B8?>:070=89:

=54>=>H5=8< =>2>=0@>465=8< 2V:< ≤ 41 B8645=L 7 C@0EC20==O< B5@CB@>1=>3> @>728B:C (35AB0FV9=89 2V: + 2V: ?VA;O =0@>465==O)*;
4>=>H5=8< =>2>=0@>465=8< (2V:< ≤ 28 4=V2):

V7 3V?5@1V;V@C1V=52BO=8F5N, 3V?>0;L1C 0F84>7<,>A:V;L:8 ?@8 B0:8E AB0=0E 72O7C20==O 1V;V@C1V=C, 9<>2V@=>, ?>@CH5=5*;
O:V ?>B@51CNBL (01> >GV:CTBLAO, I> ?>B@51C20B825==>3> 22545==O ?@5?0@0BV2 :0;LFVN 01> V=DC7V9 :0;LFVT27G8=V2, >A:V;L:8 VA=CT
@878: CB2>@5==O ?@5F8?VB0BV2 :0;LFVT2>W A>;V F5DB@80:A>=C.

* # 4>A;V465==OE *Vn vitro* 1C;> ?>:070=>, I> F5DB@80:A>= <>65 28BVA=OB8 1V;V@C1V= 7V 72O7:C 7 0;L1C A8@>20B:8 :@>2V, I> ?@872>48BL 4>
<>6;82>3> @878:C @>728B:C 1V;V@C1V=>2>W 5=F5D0;>?0BVW C B0:8E ?0FVT=BV2.

5@54 2=CB@VH=L><□O7>28< 22545==O< F5DB@80:A>=C A;V4 >1>2O7:>2> 28::NG8B8 =0O2=VABL ?@>B8?>:070=L 4> 70AB>AC20==O
;V4>:0W=C, O:I> 9>3> 70AB>A>2CNBL O: @>7G8==8: (482. V=AB@C:FVN 4;O <548G=>3> 70AB>AC20==O ;V4>:0W=C, >A>1;82> ?@>B8?>:070==O).
>7G8=8 F5DB@80:A>=C, I> :0W=, =V:>;8 =5 A;V4 22>48B8 2=CB@VH=L>25==>.

70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9.

>7G8==8:8, I> 7G8= V=35@0 01> @>7G8= 0@B<0=0, =5 A;V4 28:>@8AB>2C20B8 4;O 2V4=>2;5==O ?@5?0@0BC &5D0:A>= C D;0:>=0E 01> 4;O
?>40;LH>3> @>72545==O 2V4=>2;5=>3> @>7G8=C 4;O 2=CB@VH=L>25==>3> 22545==O, >A:V;L:8 <>65 CB2>@8B8AO ?@5F8?VB0B. @5F8?VB0B8
:0;LFVT2>W A>;V F5DB@80:A>=C B0:>6 <>6CBL CB2>@N20B8AO ?@8 7=C V7 :0;LFVT2= =5 <>6=0 22>48B8 >4=>G0A=> V7 @>7G8=0<8 4;O
2=CB@VH=L>25==>3> 22545==O, I> 7G8=8 <>6=0 22>48B8 ?>A;V4>2=>, >48= ?VA;O >4=>3>, O:I>N @V48=>N. # 4>A;V465==OE *Vn vitro* V7
28:>@8AB0==O< ?;07<8 ?C?>28==>W :@>2V 4>@>A;8E B0 =>2>=0@>465=8E 1C;> ?>:070=>, I> =>2>=0@>465=8< 703@>6CT ?V428I5=89 @878:
CB2>@5==O ?@5F8?VB0BV2 :0;LFVT2>W A>;V F5DB@80:A>=C.

!CAC20==O ?@5?0@0BC V7 ?5@>@0;L=8<8 0=B8:>03C;O=B0<8 <>65 ?>A8;N20B8 5D5:B ?@>B8 2VB02>B5GV. 5:<5=4CTBLAO G0AB>
?5@52V@OB8 4=5 =>@<0;V7>20=5 A?V22V4=>H5==O B0 =0;56=8< G8=>< :>@53C20B8 4>7C 0=B82VB0=>

A=CNBL AC?5@5G;82V 40=V I>4> ?>B5=FV9=>3> ?>A8;5==O B>:A8G=>3> 2?;82C 0B;V:>784V2 =0 =8@:8 ?@8 WE 70AB>AC20==V @07< V7
F5D0;>A?>@8=0<8. B0:8E 28?04:0E A;V4 @5B5;L=> 4>B@8<5=40FV9 V7 <=>VB>@8=3C @V2=O 03;V:>784V2 (B0 DC=:FVW =8@>:) C :;V=VG=V9
?@0:B8FV.

4>A;V465==V *in vitro* ?@8 70AB>AC20==V E;>@0;C C :<1V=0FVW V7 F5DB@80:A>=< A?>AB5@V30;8AO 0=B03>=VAB8G=V 5D5:B8. ;V=VG=0
7=0GCIVABL F8E 40=8E =52V4<0.

5 1C;> 70@5TAB@>20=> 28?04:V2 270T<>4VW =>< B0 :0;LFVT2=>< 4;O 2=CB@VH=L><O7>2>3> 22545==O B0 :0;LFVT2

?0FVT=BV2, O:V 70AB>A>2CNBL F5DB@80:A>=, <>6;82V E81=>?>78B82=V @57C;LB0B8 B5ABC C<1A0.

&5DB@80:A>=, O: V V=HV 0=B81V>B8:8, <>65 A?@8G8=OB8 E81=>?>78B82=V @57C;LB0B8 0=0;V7C =0 30;0:B>75

>4V1=8< G8=><, ?@8 287=0G5==V 3;N:>78 C A5GV 70 4>?><3>N =5D5@<5=B=8E <5B>4V2 @57C;LB0B8 <>6CBL 1CB8 E81=>?>78B82=8<8. FVTW
?@8G8=8 2 ?5@V>4 70AB>AC20==O F5DB@80:A>=C A;V4 287=0G0B8 @V25=L 3;N:>78 C A5GV 70 4>?><3>N D5@<5=B=8E <5B>4V2.

>@CH5=L DC=:FVW =8@>: =5 A?>AB5@V30;>AO ?VA;O AC?CB=L>3> 70AB>AC20==O 25;8:8E 4>7 F5DB@80:A>=C B0 ?>BC6=8E 4VC@5B8:V2
(=0?@8::04, DC@>A5

4=>G0A=5 70AB>AC20==O ?@>15=5F84C =5 7=86CT 282545==O F5DB@80:A>=C.

A>1;82>ABV 70AB>AC20==O.

50:FVW 3V?5@GCB;82>ABV.

/: V ?@8 70AB>AC20==V 2AVE β-;0:B0<=8E 0=B81V>B8:V2, ?>2V4<×;O;>AO ?@> 28?04:8 A5@9>7=8E @50:FV9 3V?5@GCB;82>ABV, V=>4V V7 ;5B0;L=8<8 =0A;V4:0<8. # 28?04:C BO6:8E @50:FV9 3V?5@GCB;82>ABV 70AB>AC20==O F5DB@80:A>=C A;V4 =5309=> ?@8?8=8B8 B0 268B8 =0;56=8E =52V4;:04=8E 70E>4V2. 5@54 ?>G0B:<×;V:C20==O A;V4 2AB0=>28B8, G8 T C ?0FVT=B0 2 0=0<=57V BO6:V @50:FVW 3V?5@GCB;82>ABV 4> F5DB@80:A>=C, V=H8E F5D0;>A?>@8=V2 01> V=H8E B8?V2 β-;0:B0<=8E 70A>1V2. !;V4 7 >15@56=VABN 70AB>A>2C20B8 F5DB@80:A>= ?0FVT=B0< V7 =0O2=VABN 2 0=0<=57V =5BO6:>W 3V?5@GCB;82>ABV 4> V=H8E β-;0:B0<=8E ?@5?0@0BV2.

0@5TAB@>20=V 28?04:8 BO6:8E =51060=8E @50:FV9 7 1>:C H:V@8 (A8=4@<×!BV25=A0-6>=A>=0 01> A8=4@<× 09T;0/B>:A8G=89 5?V45@<0;L=89 =5:@>;V7); >4=0: G0AB>B0 F8E O28I =52V4<×(0)

70T<>4VO V7 ;V:0@AL:8<8 70A>10<8, I>

*# =54>=>H5=8E B0 4>=>H5=8E =5<>2;OB 2V:<× <5=H5 1 ?8A0=V 28?04:8 CB2>@5==O ?@5F8?VB0BV2 :0;LFVT2>W A>;V F5DB@80:A>=C C ;535=OE B0 =8@:0E V7 ;5B0;L=8<8 =0A;V4:0<8.)>=09<5=H5 >4>=> B0 :0;LFV9 22>48;8 C @V7=89 G0A B0 G5@57 @V7=V 2=CB@VH=L>25==V V=DC7V9=V A8AB5<8. 3V4=> V7 =0O2=8<8 =0C:>28<8 40=8<8, =5 70@5TAB@>20=> ?V4B25@465=8E 28?04:V2 CB2>@5==O 2=CB@VH=L>AC48==8E ?@5F8?VB0BV2, :@V< O: C =>2>=0@>465=8E, O:8< 22>48;8 F5DB@80:A>= B0 :0;LFVT27G8=8 01> 1C4L-O:V V=HV :0;LFVT2A;V465==OE *Vn vitro* 1C;> ?>:070=>, I> =>2>=0@>465=8< 703@>6CT ?V428I5=89 @878: CB2>@5==O ?@5F8?VB0BV2 :0;LFVT2>W A>;V F5DB@80:A>=C ?>@V2=O=> V7 ?0FVT=B0<8 V=H8E 2V:>28E 3@C?.*

@8 70AB>AC20==V F5DB@80:A>=C ?0FVT=B0< 1C4L-O:>3> 2V:C ?@5?0@0B =5 <>6=0 7 22>48B8 >4=>G0A=> V7 1C4L-O:8<8 @>7G8=0<8 4;O 2=CB@VH=L>25==>3> 22545==O, I> @8AB0==V @V7=8E V=DC7V9=8E A8AB5< 01> 22545==V ?@5?0@0BV2 C @V7=V V=DC7V9=V 4V;O=:8. @>B5 ?0FVT=B0< 2V:<× AB0@H5 28 4=V2 F5DB@80:A>= B0 :0;LFVT27G8=8 <>6=0 22>48B8 ?>A;V4>2=>, >48= ?VA;O >4=>3>, 70 C<>28 22545==O ?@5?0@0BV2 G5@57 @V7=V V=DC7V9=V A8AB5<8 C @V7=V 4V;O=:8 BV;0 01> 70B> ?@><820==O V=DC7V9=>W A8AB5<8 7G8=V2 4;O ?>2=>3> ?0@5=B5@0;L=>3> E0@GC20==O (%), <548G=V ?@0FV2=8:8 <>6CBL ?@87=0G8B8 0;LB5@=0B82=V 0=B810:B5@V0;L=V 70A>18, 70AB>AC20==O O:8E =5 ?>2O70=5 V7 ?>4V1=8< @878:<× CB2>@5==O ?@5F8?VB0BV2. /:I> 70AB>AC20==O F5DB@80:A>=C ?0FVT=B0<, O:V ?>B@51CNBL ?>ABV9=>3> E0@GC20==O, 287=0=> =5>1EV4=8<, @>7G8=8 4;O % B0 F5DB@80:A>= <>6=0 22>48B8 >4=>G0A=>, E>G0 V G5@57 @V7=V V=DC7V9=V A8AB5<8 B0 C @V7=V 4V;O=:8 BV;0. "0:>6 22545==O @>7G8=V2 4;O %<>6=0 ?@87C?8=8B8 =0 G0A V=DC7VW F5DB@80:A>=C B0 ?@><8B8 V=DC7V9=V A8AB5<8

VB8.

57?5:0 B0 5D5:B82=VABL &5D0:A>=C C =>2>=0@>465=8E, =5<>2;OB B0 4VB59 1C;8 2AB0=>2;5=V 4;O 4>7, >?8A0=8E C @>74V;V «!>AV1 70AB>AC20==O B0 4>78». # 4>A;V465==OE 1C;> ?>:070=>, I> F5DB@80:A>=, O: 45O:V V=HV F5D0;>A?>@8=8, <>65 28BVA=OB8 1V;V@C1V= 7V 72O7:C V7 0;L1C< A8@>20B:8 :@>2V.

&5D0:A>= ?@>B8?>:070=89 =54>=>H5=8< B0 4>=>H5=8< =>2>=0@>465=8<, O:8< 703@>6CT @878: @>728B:C 1V;V@C1V=>2>W 5=F5D0;>?0BVW. >?>A5@54:>20=0 35<>;VB8G=0 0=5

8?04:8 V>?>A5@54:>20=>W 35<>;VB8G=>W 0=5AB5@V30;8AO C ?0FVT=BV2, O:V >B@818 ::0AC F5D0;>A?>@8=V2, 2 B>=. "O6:V 28?04:8 35 <>;VB8G=>W 0=5

/:I> ?V4 G0A 70AB>AC20==O F5DB@80:A>=C C ?0FVT=B0 28=8:0T 0=573;O=CB8 4V03=>7 0=5FV9>20=>W V7 70AB>AC20==O< F5D0;>A?>@8=C, B0 ?@8?8=8B8 70AB>AC20==O F5DB@80:A>=C 4> 2AB0=>2;5==O 5BV>;>3VW 70E2>@N20==O.

>23>B@820;5 ;V:C20==O.

@8 4>23>B@820;> ?@>2>48B8 @>73>@=CB89 0=0;V7 :@>2V.

>;VB/=04>@30=V7

8?04:8 :>;VBC B0 ?A524><5<1@0=>7=>3> :>;VBC, 0A>FV9>20=8E V7 70AB>AC20==O< 0=B810:B5@V0;L=8E 70A>1V2, 1C;8 70@5TAB@>20=V =0
B;V 70AB>AC20==O <0965 2AVE 0=B810:B5@V0;L=8E 70A>1V2, 2 B>=C. "O6:VABL F8E 70E2>@N20=L<>65 :>;820B8AO 2V4 ;53:>W 4>
703@>7;82>W 4;O 68BBO. "> 2@0E>2C20B8 <>6;82VABL B0:>3> 4V03=>7C C ?0FVT=BV2, C O:8E ?V4 G0A 01> ?VA;O 70AB>AC20==O
F5DB@80:A>=C 28=8:;0 4V0@5O. !;V4 >1=>< B0 70AB>AC20==O 2V4?>2V4=8E 70A>1V2 ?@>B8 *Clostridium difficile* V:0@AL:V 70A>18, I>
?@83=VGCNBL ?5@8AB0;LB8:C, 70AB>A>2C20B8 =5 A;V4.
/: V ?@8 70AB>AC20==V V=H8E 0=B810:B5@V0;L=8E 70A>1V2, <>6CBL 28=8:0B8 AC?5@V=D5:FVW, A?@8G8=5=V =5GCB;828<8 4> ?@5?0@0BC
>@30=V7<0<8.
"O6:0 =8@:>20 B0 ?5GV=:>20 =54>AB0B=VABL.
28?04:C BO6:>W =8@:>2>W B0 ?5GV=:>2>W =54>AB0B=>ABV @5:>5=4>20=89 @5B5;L=89 ;V=VG=89 <=>VB>@8=3 157?5:8 B0 5D5:B82=>ABV
?@5?0@0BC.
?;82 =0 @57C;LB0B8 A5@>;>3VG=8E 4>A;V465=L.
@8 70AB>AC20==V ?@5?0@0BC &5D0:A>= B5AB C<1A0 <>65 4020B8 E81=>?>78B82=V @57C;LB0B8. "0:>6 &5D0:A>= <>65 A?@8G8=OB8
E81=>?>78B82=V @57C;LB0B8 0=0;V7C =0 =0O2=VABL 30;0:B>75
@8 287=0G5==V 3;N:>78 C A5GV =5D5@<5=B=8<8 <5B>40<8 <>6CBL 1CB8 >B@8<0=V E81=>?>78B82=V @57C;LB0B8. @>BO3< 70AB>AC20==O
&5D0:A>=C @V2=V 3;N:>78 C A5GV A;V4 287=0G0B8 70 4>?><3>N D5@<5=B=8E <5B>4V2 0=0;V7C.
! ?5:B@ 0=B810:B5@V0;L=>W 0:B82=>ABV.
&5DB@80:A>= <0T>1<565=89 A?5:B@ 0=B810:B5@V0;L=>W 0:B82=>ABV V<>65 1CB8 =5?@840B=8< 4;O 70AB>AC20==O 2 O:>ABV
<=>B5@0?VW ?@8 ;V:C20==V ?52=8E B8?V2 V=D5:FVW, :@V< 28?04:V2, :>;8 71C4=8: 265 ?V4B25@465=89. # 28?04:C ?>;V1=8E V=D5:FV9, :>;8
A5@54 ?V4>7@N20=8E 71C4=8:V2 T @578AB5=B=V 4> F5DB@80:A>=C>@30=V7<8, A;V4 @>73;O=CB8 70AB>AC20==O 4>40B:>28E 0=B81V>B8:V2.
0AB>AC20==O ;V4>:0W=C.
/:I> 2 O:>ABV @>7G8=8:0 70AB>A>2CNBL @>7G8= ;V4>:0W=C, F5DB@80:A>= <>6=0 22>48B8 ;8H5 2=CB@VH=L<>O7>2>. 5@54 22545==O<
?@5?0@0BC A;V4 >1>2O7:>2> 2@0EC20B8 ?@>B8?:>070==O 4> 70AB>AC20==O ;V4>:0W=C, 70AB5@565==O B0 V=HC 2V4?>2V4=C V=D>@<0FVN,
=02545=C C V=AB@C:FVWW 4;O <548G=>3> 70AB>AC20==O ;V4>:0W=C. >7G8= ;V4>:0W=C C 6>4=>
>2G=>:0<O=0 E2>@>10.
28?04:C =0O2=>ABV =0 A>=>3@0B0 WE 28=8:=5==O 7@>AB0;0 ?@8 70AB>AC20==V F5DB@80:A>=C C 4>7V 1 3 =0 4>1C B0 28I5. A>1;82>W
>15@56=>ABV A;V4 4>B@8AC20==V ?@5?0@0BC 4VBO=>@5==O ?@5F8?VB0BV2 :0;LFVT2>W A>;V F5DB@80:A>=C AC?@>2>46C20;>AO A8
<0B8:>N. 0 =0O2=>ABV A8<5=4CTBLAO :>=A5@20B82=5 =5EV@C@3VG=5 ;V:C20==O, V ;V:0@<0T ?@89=OB8 @VH5==O ?@> ?@8?8=5==O
70AB>AC20==O ?@5?0@0BC, A?8@0NG8AL =0 @57C;LB0B8 >FV=:8 :>@8ABV-@878:C :>=:@5B=>3> 28?04:C.
>2G=89 AB07.
8?04:8 ?0=:@50B8BC, <>6;82> A?@8G8=5=V =5?@>EV4=VABN 6>2G=8E H;OEV2, 1C;8 70@5TAB@>20=V C ?0FVT=BV2, O:V >B@8. V;LHVABL V7
B0:8E ?0FVT=BV2 <0;8 D0:B>@8 @878:C @>728B:C E>;5AB07C B0 CB2>@5==O 1V;V0@=>3> A;046C, B0:V O: ?>?5@54=O 7=0G=0 B5@0?VO, BO6:0
E2>@>10 B0 ?>2=5 ?0@5=B5@0;L=5 E0@GC20==O. 5 <>6=0 28:;NG0B8, I> V=VFNNG8< 01> 4>40B:>28< D0:B>@< @>728B:C FL>3> ?>@CH5==O
<>65 1CB8 CB2>@5==O C 6>2G=8E H;OE0E ?@5F8?VB0BV2 2=0A;V4>: 70AB>AC20==O &5D0:A>=C.
8@:>2>:0<O=0 E2>@>10.
0@5TAB@>20=V 28?04:8 CB2>@5==O =8@:>28E :0<5=V2, I> 7=8:0;8 ?VA;O ?@8?8=5==O 70AB>AC20==O F5DB@80:A>=C. # 28?04:C =0O2=>ABV A8
18B8 C;LB@072C:>25 >1AB565==O. VH5==O I>4> 70AB>AC20==O ?@5?0@0BC ?0FVT=B0< V7 =0O2=VABN 2 0=0<=57V =8@:>28E :0<5=V2 01>
3V?5@:0;LFVC@VW ?@89<0T ;V:0@, A?8@0NG8AL =0 @57C;LB0B8 >FV=:8 :>@8ABV-@878:C :>=:@5B=>3> 28?04:C.
#B8;V70FVO ;V:0@AL:>3> 70A>1C.

04E>465==O ;V:0@AL:>3> 70A>1C C 7>2=VH=T A5@54>28I5 A;V4 725AB8 4>1V30B8 ?>B@0?;O==N ;V:0@AL:>3> 70A>1C C :0=0;V70FV9=C A8AB5
4><0H=V 2V4E>48. C4L-O:89 =528:>@8AB0=89 ;V:0@AL:89 70AV1 ?VA;O 70:V=G5==O ;V:C20==O 01> B5@ABV A;V4 ?>25@=CB8 2 >@83V=0;L=V9
C?0:>2FV ?>AB0G0;L=8:C (;V:0@N 01> D0@<0F52BC) 4;O ?@028;L=>W CB8;V70FVW.

0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.

03VB=VABL.

&5DB@80:A>= ?@>=8:0T G5@57 ?;0F5=B0@=89 10@T@. A=CNBL >1<565=V 40=V I>4> 70AB>AC20==O F5DB@80:A>=C 203VB=84 203VB=>ABV,
7>:@5<0 C B@8<5AB@V, F5DB@80:A>=<6=0 70AB>A>2C20B8, ;8H5 O:I> :>@8ABL ?5@528ICT @878:.

>4C20==O 3@C44N.

&5DB@80:A>= ?@>=8:0T C 3@C4=5 <>;> C =87L:8E :>=F5=B@0FVOE, 0;5 ?@8 70AB>AC20==V ?@5?0@0BC C B5@0?52B8G=8E 4>70E =5
>GV:CTBLAO 6>4=>3> 2?;82C =0 3@C4=8E =5<>2;OB. @>B5 =5 <>6=0 28;;NG0B8 @878: @>728B:C 4V0@5W B0 3@81:>2>W V=D5:FVW A;87>28E
>1>;>=>.: !;V4 2@0E>2C20B8 <>6;82VABL A5=A81V;V70FVW. >B@V1=> ?@89=OB8 @VH5==O I>4> ?@8?8=5==O 3>4C20==O 3@C44N 01>
?@8?8=5==O/2V4<>28 2V4 70AB>AC20==O F5DB@80:A>=C V7 2@0EC20==O< :>@8ABV 2V4 3@C4=>3> 283>4>2C20==O 4;O 48B8=8 B0 :>@8ABV
2V4 B5@0?VW 4;O 6V=:8.

\$5@B8;L=VABL.

4>A;V465==OE @5?@>4C:B82=>W DC=:FVW =5 1C;> 28O2;5=> >7=0: =51060=>3> 2?;82C =0 G>;>2VGC 01> 6V=>GC D5@B8;L=VABL.

40B=VABL 2?;820B8 =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B< 01> V=H8<8 <5E0=V7<0<8.

V4?>2V4=V 4>A;V465==O =5 ?@>2>48;8AO. # 72O7:C 7 <>6;82VABN 28=8:=5==O B0:8E ?>1VG=8E @50:FV9, O: 70?0<>@>G5==O, &5D0:A>= <>65
2?;820B8 =0 740B=VABL :5@C20B8 02B>B@0=A?>@B< 01> V=H8<8 <5E0=V7<0<8.

!?!>AV1 70AB>AC20==O B0 4>78.

5@54 22545==O< =5>1EV4=> ?@>25AB8 H:V@=V ?@>18 =0 V=482V4C0;L=C GCB;82VABL 4> F5DB@80:A>=C B0 ;V4>:0W=C (?@8 2=CB@VH=L>
<□O7>2>.

>@>A;V B0 4VB8 2V:>< 2V4 12 @>:V2: ?@87=0G0B8 1-2 3 &5D0:A>=C 1 @07 =0 4>1C (:>6=V 24 3>48=8). @8 B06:8E V=D5:FVOE 01> V=D5:FVOE,
71C4=8:8 O:8E <0NBL ;8H5 ?> F5DB@80:A>=C, 4>1>2C 4>7C <>6=0 71V;LHC20B8 4> 4 3.

>2>=0@>465=V, =5<>2;OB0 B0 4VB8 2V:>< 4> 12 @>:V2.

86G5 =02>4OBLAO @5:><5=4>20=V 4>78 4;O 70AB>AC20==O 1 @07 =0 4>1C.

>2>=0@>465=V (4> 2 B86=V2): 20-50 <3/:3 <0A8 BV;0 1 @07 =0 4>1C, 4>1>20 4>70 =5 <0T ?5@528IC20B8 50 <3/:3 <0A8 BV;0. @8 287=0G5==V 4>78
?@5?0@0BC 4;O 4>=>H5=8E V =54>=>H5=8E 4VB59 2V4AB59 =5<0T.

&5D0:A>= ?@>B8?>:070=89 4;O 70AB>AC20==O =>2>=0@>465=8< 2V:< ≤ 28 4=V2 ?@8 =5>1EV4=>ABV (G8 >GV:C20=V9 =5>1EV4=>ABV)
;V:C20==O 2=CB@VH=L>25==8<8 @>7G8=0<8, O:V ABV9=V 2=CB@VH=L>25==V 2;820==O, O:V < 28=8:=5==O ?@5F8?VB0BV2 :0;LFVT28E A>;59
F5DB@80:A>=C.

>2>=0@>465=V B0 4VB8 2V:>< 2V4 15 4=V2 4> 12 @>:V2: 20-80 <3/:3 <0A8 BV;0 1 @07 =0 4>1C.

VBO< V7 <0A>N BV;0 ?>=04 50 :3 ?@87=0G0B8 4>78 4;O 4>@>A;8E.

=CB@VH=L>25==V 4>78 50 <3/:3 01> 28IV A;V4 22>48B8 H;OE< V=DC7VW C?@>4>26 ?@8=09<=V
30 E28;8=.

%2>@V;VB=L>3> 2V:C.
 %2>@8<;VB=L>3> 2V:C :>@5:FVO 4>78 =5 ?>B@V1=0.
 "@820;VABL;V:C20==O.
 "@820;VABL;V:C20==O 70;568BL 2V4 ?>:070==O B0 ?5@51V3C E2>@>18.
 ><IV=>20=0 B5@0?VO.
 >A;V465==O ?>:070;8, I> 2V4=>A=> 1030BL>E 3@0<=530B82=8E 10:B5@V9 VA=CT A8=5@3V7<=>< V 03;V:>7840<8. 572060NG8 =0 B5, I> ?V428I5=C
 5D5:B82=VABL B0:8E :<1V=0FV9 =5 702648 <>6=0 ?5@5410G8B8, WW A;V4<0B8 =0 C207V ?@8 =0O2=>ABV BO6:8E, 703@>7;828E 4;O 68BBO
 V=D5:FV9, A?@8G8=5=8E *Pseudomonas aeruginosa*. '5@57 DV78G=C =5AC=C B0 03;V:>784V2 WE A;V4 22>48B8 >:@5<> 2 @5:<<5=4>20=8E 4>70E.
>7C20==O 2 >A>1;828E 28?04:0E.
 5=V=3VB.
 @8 10:B5@V0;L=>

<i>Neisseria meningitidis</i>	4 4=V
<i>Haemophilus influenzae</i>	6 4=V2
<i>Streptococcus pneumoniae</i>	7 4=V2

>@5;V>7 □09<0: 4>@>A;8< B0 4VBO< 50 <3/:3 (=0928I0 4>1>20 4>70 2 3) 1 @07 =0 4>1C ?@>BO3><
 14 4=V2.
 >=>@5O.
 ;O ;V:C20==O 3>=>@5W (A?@8G8=5=>W CB2>@NNG8<8 B0 =5CB2>@NNG8<8 ?5=VF8;V=07C HB0<0<8) @5:<<5=4CTBLAO ?@87=0G0B8 @07>2C
 4>7C 250 <3 2=CB@VH=L><□O7>2>.
 @>DV;0:B8:0 V=D5:FV9 C EV@C@3VW.
 ;O ?@>DV;0:B8:8 ?VA;O>?5@0FV9=8E V=D5:FV9 ?@8 :>=B020=8E 01> ?>B5=FV9=> :>=B020=8E EV@C@3VG=8E 2B@CG0==OE @5:<<5=4>20=>
 70;56=> 2V4 ABC?5=O =5157?5:8 70@065==O 22>48B8 @07>2C 4>7C 1-2 3 ?@5?0@0BC 70 30-90 E28;8= 4> ?>G0B:C >?5@0FVW. @8 >?5@0FVOE =0
 B>2ABV9 V ?@O1@5 70@5:<<5=4C20;> A515 >4=>G0A=5 22545==O &5D0ABC B0 >4=>3> 7 5=VB@>V;V2, =0?@8::04, >@=V407>;C.
 >@CH5==O DC=:FV9 =8@>: B0 ?5GV=:8.
 # E2>@8E V7 ?>@CH5==O<8 DC=:FV9 =8@>: =5<0T =5>1EV4=>ABV 7=86C20B8 4>7C 2 B> DC=:FVO ?5GV=:8 70;8H0TBLAO =>@<0;L=>N. 8H5 C
 @07V =8@:>2>W =54>AB0B=>ABV 2 ?5@54B5@
 %2>@8<, O:V 7=0E>4OBLAO =0 4V0;V7V, =5<0T ?>B@518 2 4>40B:>2>4=0: :>=B@>;N20B8 :>=F5=B@0FVN F5DB@80:A>=C 2 A8@>20BFV :@>2V,
 >A;V;L:8 C F8E E2>@8E <>65 7=86C20B8AO H284:VABL 282545==O. >1>20 4>70 &5D0ABC C E2>@8E, O:V 7=0E>4OBLAO =0 4V0;V7V, =5<0T
 ?5@528IC20B8 2 3.
 # E2>@8E V7 ?>@CH5==O<8 DC=:FV9 ?5GV=:8 =5<0T =5>1EV4=>ABV 7=86C20B8 4>7C 2 B> DC=:FVO =8@>: 70;8H0TBLAO =>@<0;L=>N.
 @8 >4=>G0A=> BO6:>@CH5==V DC=:FV9 =8@>: B0 ?5GV=:8 A;V4 @53C;O@=> 287=0G0B8 :>=F5=B@0FVN F5DB@80:A>=C 2 ?;072V B0
 ?@>2>48B8 :>@5:FVN 4>78 ?@5?0@0BC 2 @07V =5>1EV4=>ABV, >A;V;L:8 @V25=L 282545==O C B0:8E ?0FVT=V2<>65 7=86C20B8AO.
 @83>BC20==O @>7G8=V2.
 V4=>2;5=V @>7G8=8 A;V4 28:>@8AB0B8 >4@07C ?VA;O ?@83>BC20==O.
 0;56=> 2V4 :>=F5=B@0FVW :>;V@ @>7G8=V2 <>65 20@VN20B8 2V4 1;V4>-6>2B>3> 4> 1C@HB8=>2>3>. &O 2;0AB82VABL 0:B82=>W @5G>28=8 =5
 2?;820T =0 5D5:B82=VABL 01> ?5@5=>A8
 =CB@VH=L><O7>20 V=T:FVO.

;O 2=CB@VH=L><O7>2>W V=T:FVW 1 3 @>7G8=OB8 C 3,5<; 1 % @>7G8=C ;V4>:0W=C; V=T:FVN @>18B8 C F5=B@ 25;8:>3><O7C. 5:>
<5=4CTBLAO 22>48B8 =5 1V;LH5 1 3 2 >4=C 4V;O=:C.
/:I> ;V4>:0W= 70AB>A>2CNBL O: @>7G8==8:; >B@8<0=89 @>7G8= =V:>;8 =5 A;V4 22>48B8 2=CB@VH=L>25==>. ;O 45B0;L=>W V=D>@<0FVW
@5:><5=4CTBLAO >7=09><8B8AO 7 V=AB@C:FVTN 4;O <548G=>3> 70AB>AC20==O ;V4>:0W=C.
0AB>AC20==O ;V4>:0W=C ?5@5410G0T ?>?5@54=T ?@>2545==O ?@>18 4;O 287=0G5==O V=482V4C0;L=>W GCB;82>ABV 4> FL>3> ;V:0@AL:>3>
70A>1C.
=CB@VH=L>25==0 V=T:FVO.
;O 2=CB@VH=L>25==>W V=T:FVW A;V4 @>7G8=8B8 1 3 &5D0:A>=C 2 10<; 2>48 4;O V=T:FV9; 22>48B8 2=CB@VH=L>25==> ?>2V;L=> (2-4
E28;8=8).
=CB@VH=L>25==5 2;820==O.
=CB@VH=L>25==5 2;820==O <0T B@820B8 =5 <5=H5 30 E28;8=. ;O ?@83>BC20==O @>7G8=C 4;O 2;820==O @>7G8=8B8 2 3 ?@5?0@0BC 2 40 <;
>4=>3> 7 =0ABC?=8E V=DC7V9=8E @>7G8=V2, 2V;L=8E 2V4 V=>V2 :0;LFVN: 0,9 % E;>@84 =0B@VN, 0,45 % E;>@84 =0B@VN + 2,5 % 3;N:>70, 5 %
3;N:>70, 10 % 3;N:>70, 6 % 45:AB@0= C @>7G8=V 3;N:>78 5 %, 6-10 % 3V4@>:A85B8;L>20=89 :@>E<0;L, 2>40 4;O V=T:FV9. 2060NG8 =0 <>6;82C
=5AC7G8=8, O:V =, =5 <>6=0 77G8=0<8, O:V B8:8, O: ?@8 ?@83>BC20==V, B0: V ?@8 22545==V.
4=0: 2 3 F5DB@80:A>=C B0 1 3 >@=V407>;C DV78G=> B0 EV AC
5 <>6=0 28:>@8AB>2C20B8 @>7G8==8:8, O:V 7G8= V=35@0 G8 @>7G8= 0@B<0=0, 4;O @>7G8=5==O &5D0:A>=C C D;0:>=0E G8 4;O @>72545==O
2V4=>2;5=>3> @>7G8=C 4;O 2=CB@VH=L>25==>3> 22545==O C 7207:C 7 2V@>3V4=VABN CB2>@5==O ?@5F8?VB0BV2 :0;LFVT28E A>;59
F5DB@80:A>=C. 8=8:=5==O ?@5F8?VB0BV2 :0;LFVT28E A>;59 F5DB@80:A>=C B0:>6 <>65 2V41C20B8AO ?@8 7= 7 @>7G8=0<8, O:V 4=V9
V=DC7V9=V9 A8AB525==>3> 22545==O. &5D0:A>= =5 <>6=0 >4=>G0A=> 22>48B8 2=CB@VH=L>25==> 7 @>7G8=0<8, O:V <=>2>=0@>465=8E,
&5D0:A>= B0 :0;LFVT27G8=8 <>6=0 22>48B8 ?>A;V4>2=>, O:I> V=DC7V9=C A8AB5 ?@><8B8

VB8.

@5?0@0B 70AB>A>2C20B8 4VBO< 73V4=> 7 4>7C20==O<, 2:070=8< C @>74V;V «!?'>AV1 70AB>AC20==O B0 4>78».

5@54>7C20==O.

@07V ?5@54>7C20==O <>65 A?>AB5@V30B8AO =C4>B0, 1;N2>B0, 4V0@5O.

@07V ?5@54>7C20==O 35<>4V0;V7 G8 ?5@8B>=50;L=89 4V0;V7 =5 7<5=H0BL =04=F5=B@0FVW ?@5?0@0BC 2 ?;072V. !?5F8DVG=>3> 0=B84>BC
=5 VA=CT. V:C20==O ?5@54>7C20==O A80B8G=5.

>1VG=V @50:FVW.

51060=8<8 @50:FVO<8, I> =09G0ABVH5 A?>AB5@V30;8AO ?@8 70AB>AC20==V F5DB@80:A>=C, T 5>78=>DV;VO, ;59:>?5=VO, B@>
<1>F8B>?5=VO, 4V0@5O, 28A8? B0 ?V428I5==O @V2=O ?5GV=:>28E D5@<5=BV2.

=D5:FVW B0 V=207VW: 3@81:>2V V=D5:FVW AB0B528E >@30=V2, ?A524<5<1@0==89 :>;VB, AC?5@V=D5:FVW.

I>:C A8AB5<8 :@>2V B0 ;VW A8AB5<8: 5>78=>DV;VO, ;59:>?5=VO, B@><1>F8B>?5=VO, 3@0=C;>F8B>?5=VO, 0=57;048 :>03C;OFVW, 35<>;VB8G=0
0=5F8B>7.

I>:C VW A8AB5<8: 0=0DV;0:B8G=89 H>;, 0=0DV;0:B8G=V @50:FVW, 0=0DV;0:B>W4=V @50:FVW, 3V?5@GCB;82VABL.

I>:C =5@2>2>W A8AB5<8: 3>;>2=89 1V;L, 70?0<>@>G5==O, AC4<8.

I>:C >@30=V2 A;CEC: 25@BV3>.

I>:C A8AB5<8 48E0==O: 1@>=E>A?07
I>:C B@02=>3> B@0:BC: 4V0@5O, =C4>B0, 1;N20==O, ?0=:@50B8B, AB<0B8B, 3;>A8B.
I>:C 35?0B>1V;V0@=>W A8AB5<8: ?V428I5==O @V2=O ?5GV=:>28E D5@<5=BV2, ?@5F8?VB0B8 C 6>2G=>2BO=8FO.
I>:C H:V@8 V ?V4H:V@=>W ;;VB:>28=8: 28A8?, A25@1V6, :@>?82O=:0, A8=4@< !BV25=A0-6>=A>=0, B>:A8G=89 5?V45@<0;L=89 =5:@>;V7,
1030B>D>@<=0 5@8B5<0, 3>AB@89 35=5@0;V7>20=89 5:70=B5<0B>7=89 ?CABC;L>7.
I>:C A5G>284V;L=>W A8AB5<8: 35<0BC@VO, 3;N:>7C@VO, >;V3C@VO, CB2>@5==O ?@5F8?VB0BV2 C =8@:0E (>1>@>B=V).
030;L=V @>7;048 B0 @50:FVW C : D;51VB, 1V;L C
01>@0B>@=V ?>:07=8:8: ?V428I5==O @V2=O :@50B8=V=C C :@>2V, E81=>?>78B82=V @57C;LB0B8 B5ABC C<1A0, E81=>?>78B82=V @57C;LB0B8
0=0;V7C =0 30;0:B>75?>78B82=V @57C;LB0B8 =5D5@<5=B=8E <5B>4V2 287=0G5==O 3;N:>78.
=D5:FV B0 V=207VW.
8?04:8 4V0@5W ?VA;O 70AB>AC20==O F5DB@80:A>=C <>6CBL 1CB8 ?>2O70=V V7 Clostridium difficile.!.;V4 ?@87=0G8B8 2V4?>2V4=C :V;L:VABL
@V48=8 B0 5;5:B@>;VBV2.
@5F8?VB0B8 :0;LFVT2>W A>;V F5DB@80:A>=C.
V4:VA=V 28?04:8 BO6:8E =51060=8E @50:FV9, V=>4V 7 ;5B0;L=8<8 =0A;V4:0<8, 70@5TAB@>20=V C =54>=>H5=8E B0 4>=>H5=8E =>2>=0@>465=8E
(2V:<< 28 4=V2), O:8< 2=CB@VH=L>25==> 22>48;8 F5DB@80:A>= B0 ?@5?0@0B8 :0;LFVN. @8 0CB>?AVW C ;535=OE B0 =8@:0E 1C;8 28O2;5=V
?@5F8?VB0B8 :0;LFVT2>W A>;V F5DB@80:A>=C. 8A>:89 @878: CB2>@5==O ?@5F8?VB0BV2 C =>2>=0@>465=8E T =0A;V4:< WE <0;>3> >1T2V B0
4>2H>3>, =V6 C 4>@>A;8E, ?5@V>4C =0?V2282545==O F5DB@80:A>=C.
0@5TAB@>20=V 28?04:8 CB2>@5==O ?@5F8?VB0BV2 C =8@:0E, ?5@5206=> C 4VB59 2V:< 2V4 3 @>:V2, O:V >B@81>2V 4>78 ?@5?0@0BC
(=0?@8::04 ≥ 80 <3:/3/4>1C) 01> 7030;L=V 4>78 ?>=04 10 3, 0 B0:>6<0;8 4>40B:>2V D0:B>@8 @878:C (=0?@8::04 >1<565=5 A?>6820==O @V48=8 01>
?>ABV;L=89 @568<). 878: CB2>@5==O ?@5F8?VB0BV2 7@>AB0T C ?0FVT=BV2, ?>7102;5=8E @CE;82>ABV 01> C E2>@8E C AB0=V 7=52>4=5==O.
@5F8?VB0B8 <>6CBL AC?@>2>46C20B8AO A8<0<8 01> 1CB8 0A8<0B8G=8<8, <>6CBL ?@872>48B8 4> =8@:>2>W =54>AB0B=>ABV B0 0=C@VW, V
7=8:0NBL ?VA;O ?@8?8=5==O 70AB>AC20==O F5DB@80:A>=C.
0@5TAB@>20=V 28?04:8 CB2>@5==O ?@5F8?VB0BV2 :0;LFVT2>W A>;V F5DB@80:A>=C C 6>2G=>C ?0FVT=BV2, O:8< ?@5?0@0B 22>48;8 C
4>70E, 28I8E 70 AB0=40@B=C @5:<<5=4>20=C 4>7C. # 4VB59, 70 40=8<8 ?@>A?5:B82=8E 4>A;V465=L, G0AB>B0 CB2>@5==O ?@5F8?VB0BV2 ?@8
2=CB@VH=L>25==>N C 45O:8E 4>A;V465==OE ?>=04 30 %. @8 ?>2V;L=>BO3<< 20-30 E28;8=) G0AB>B0 CB2>@5==O ?@5F8?VB0BV2, >G5284=>,
=86G0. #B2>@5==O ?@5F8?VB0BV2 70728G09 =5 AC?@>2>46CTBLAO A8<0<8, 0;5 C @V4:VA=8E 28?04:0E 28=8:0;8 B0:V ;;V=VG=V A8<8 O: 1V;L,
=C4>B0 V 1;N20==O. B0:8E 28?04:0E @5:<<5=4CTBLAO A8<0B8G=5 ;V:C20==O. VA;O ?@8?8=5==O 70AB>AC20==O F5DB@80:A>=C ?@5F8?VB0B8
70728G09 7=8:0NBL.

"5@ABV.3 @>:8.

#<>28 715@V30==O.

15@V30B8 ?@8 B5@83V=0;L=V9 C?0:>2FV.

15@V30B8 C =54>ABC?=>

@83>B>2;5=89 @>7G8= 715@V30B8 =5 1V;LH5 6 3>48= ?@8 :V<=0B=V9 B548= ?@8 B5

5AC

&5D0:A>= =5 <>6=0 7

&5DB@80:A>= =5AC<, 20=:><, D;C:>=07>;>< V 03;V:>7840<8.
5 A;V4 7

#?0:>2:0.
> 1 3 ?>@>H:C C D;0:>=V, ?> 1 D;0:>=C C :0@B>==V9 C?0:>2FV.

0B53>@VO 2V4?CA:C. 0 @5F5?B>

8@>1=8:..
N?V= V

VAF57=0E>465==O 28@>1=8:0 B0 9>3> 04@5A020465==O 4VO;L=>ABV.
198-202, LN =40AB@V0; @VO 2, 0=4848? 462046 8AB 09A5= .., =4VO.