

!" #&/
4;O <548G=>3> 70AB>AC20==O ?@5?0@0BC

&\$" !-&/
(CEFTRIAZONE-DARNITSA)

!;:04:
4VNG0 @5G>28=0: ceftriazone;
1 D;0:>=C =0B@VT2>W A>;V C ?5@5@0EC20==V =0 F5DB@80:A>= 500 <3 (0,5 3) 01> 1 3.

V:0@AL:0 D>@<0. >@>H>: 4;O @>7G8=C 4;O V='T:FV9.

\$0@<0:>B5@0?52B8G=0 3@C?0. =B810:B5@V0;L=V 70A>18 4;O A8AB5<=>3> 70AB>AC20==O. =HV
15B0-;0:B0<=V 0=B81V>B8:8. ?>A?>@8=8 III ?>:>;V==O. &5DB@80:A>=. >4 "I J01D D04.

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

>:070==O.

&5DB@80:A>=-0@=8FO 70AB>A>2C20B8 4;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
H;C=:>2>-:8H:>2>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
H;C=:>2>-:8H:>2>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 ?@5?0@0BC =5>1EV4=> 4>B@8DVFV9=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. 002=VABL 2
0=0<=57V B06:8E @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 15B0-;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 V7 C@0EC20==O< AB@>:C
2=CB@VH=L>CB@>1=>3> @>728B:C (35AB0FV9=89 2V: + 2V: ?VA;O =0@>465==O). # 4>A;V465==OE
In vitro 1C;> ?>:070=>, I> F5DB@80:A>= <>65 28BVA=OB8 1V;V@C1V= 7V 7207: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.

>=>H5=8< =>2>=0@>465=8< (2V:>≤ 28 4=V2):

- V7 3V?5@1V;V@C1V=52B0=8F5N, 3V?>0;L1C 0F84>7><, >A:V;L:8 ?@8 B0:8E AB0=0E 7207C20==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 (482. @>74V;8 «A>1;82>ABV 70AB>AC20==O» B0 «>1VG=V @50:FVW»).

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 2 O:>ABV @>7G8==8:0
(482. @>74V; «A>1;82>ABV 70AB>AC20==O»). 82. 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==>.

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

>@>A;V B0 4VB8 2V:>< 2V4 12 @>:V2: ?@87=0G0B8 1-2 3 F5DB@80: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.

&5DB@80: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;LFVVT28E A>;59
F5DB@80:A>=C (482. @>74V; «@>B8?>:070==O»).

>2>=0@>465=V B0 4VB8 2V:>< 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=. >78, I> ?5@528ICNBL 80 <3/:3 <0A8 BV;0, =5 A;V4 70AB>A>2C20B8 G5@57 ?V428I5=89
@878: 6>2G=>W ?@5F8?VB0FVW.

0FVT=B8 ;VB=L>3> 2V:C.

;O ?0FVT=BV2 ;VB=L>3> 2V:C, 70 C<>28 =0;56=>3> DC=:FV>=C20==O =8@>: V ?5GV=:8,
:>@83C20==O 4>78 =5 ?>B@V1=>.

"@820;VABL ;V:C20==O.

>7C V A?>AV1 70AB>AC20==O A;V4 287=0G0B8 70;56=> 2V4 B06:>ABV V=D5:FVW, GCB;82>ABV
?0B>35==>3> >@30=V7ABV 28?04:V2 704>2V;L=V B5@0?52B8G=V @57C;LB0B8 <>6CBL 1CB8 >B@8
<0=V ?@8 70AB>AC20==O ?@5?0@0BC 1 @07 =0 4>1C.

"@820;VABL B5@0?VW 70;568BL 2V4 ?5@51V3C 70E2>@N20==O. /: ?@89=OB> ?@8 B5@0?VW
0=B81V>B8:0<8, 70AB>AC20==O ?@5?0@0BC &5DB@80:A>=-0@=8FO A;V4 ?@>4>26C20B8
?@>B03<<

48-72 3>48=?VA;O 7=8:=5==O C ?0FVT=B0 30@OG:8 01> ?VA;O >B@80==O @57C;LB0BC, I>
A2V4G8BL ?@> 10:B5@V0;L=C 5@048:0FVN.

><1V=>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 B06:8E, 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=> <5=V=3VBV C =5<>2;OB V 4VB59 2V:>< 4> 12 @>:V2 ;V:C20==O

@>7?>G8=0B8 7 4>78

100 <3/:3 (0;5 =5 1V;LH54 3) 1 @07 =0 4>1C. /: BV;L:8 71C4=8: 1C45 V45=B8DV:>20=89, 0 9>3>

GCB;82VABL 287=0G5=0, 4>7C <>6=0 2V4?>2V4=> 7=878B8. 09:@0IV @57C;LB0B8 4>AO30;8AO ?@8
B0:V9 B@820;>ABV ;V:C20==O:

Neisseria meningitidis

4 4=V

Haemophilus influenzae

6 4=V2

Streptococcus pneumoniae

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 ?@>B03>
<
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><□07>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=V9=> :=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 F5DB@80:A>=C 70 30-90 E28;8= 4> ?>G0B:C >?5@0FVW. @8 >?5@0FV9=0
B>2ABV9 V ?@01@5 70@5:><5=4C20;> A515 >4=>G0A=5 22545==O F5DB@80:A>=C 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 3.
%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 ?@5?0@0BC 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=>@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.
=CB@VH=L><07>20 V=T:FVO.
;O 2=CB@VH=L><07>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> <07C. !;V4 22>48B8 =5 1V;LH5 1 3 2 >4=C 4V;O=C.
/:I> ;V4>:0W= 70AB>A>2CNBL 2 O:>ABV @>7G8==8:0, >B@8<0=89 @>7G8= =V:>;8 =5 A;V4 22>48B8
2=CB@VH=L>25==> (4828AL @>74V; «@>B8?>:070==O»). ;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 F5DB@80: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
F5DB@80: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=C 7 @>7G8=0<8, O:V 4=V9 V=DC7V9=V9 A8AB525==>3> 22545==O. @5?0@0B
=5 <>6=0 >4=>G0A=> 22>48B8 2=CB@VH=L>25==> 7 @>7G8=0<8, O:V <=>2>=0@>465=8E,
F5DB@80:A>= B0 :0;LFVT27G8=8 <>6=0 22>48B8 ?>A;V4>2=>, O:I> V=DC7V9=C A8AB5 ?@><8B8

>1VG=V @50:FVW.

=D5:FVW: 7 AB0B528E H;OEV2, <>6;820 AC?5@V=D5:FVO @V7=>W ;>:0;V70FVW, A?@8G8=5=0
4@V6460<8, 3@81:0<8 01> V=H8<8 @578AB5=B=8<8 >@30=V7<0<8.
I>:C A8AB5<8 :@>2V B0 ;VW A8AB5<8: =59B@>?5=VO, ;59:>?5=VO, 3@0=C;>F8B>?5=VO,
5>78=>DV;VO, B@><1>F8B>?5=VO, 0=5;=>30FVO ?@>B@><1V=>2>3> G0AC, ?>@CH5==O
:>03C;OFVW, 03@0=C;>F8B>7. V4 G0A B@820;>3> ;V:C20==O A;V4 @53C;O@=> :>=B@>;N20B8
:0@B8=C :@>2V.
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 B0 @V2=>2038: 25@BV3>.
I>:C >@30=V2 48E0==O, 3@C4=>W ;;VB:8 B0 A5@54>ABV==O: 1@>=E>A?07
I>:C B@02=>3> B@0:BC: AB<0B8B, 3;>A8B, =5>D>@<;5=89 :0; 01> 4V0@5O, =C4>B0, 1;N20==O,
?0=:@50B8B (<>6;82>, A?@8G8=5=89 >1AB@C:FVTN 6>2G=8E ?@>B>:V2). "0:V ?>1VG=V @50:FVW,
O: ?@028;>; ;53:V V G0AB> 7=8:0NBL ?@>BO3< 01> ?VA;O?@8?8=5==O ;V:C20==O. A524<5
<1@0=>7=89 :>;VB, 7451V;LH>3> A?@8G8=5=89 Clostridium difficile V;LHVABL V7 F8E E2>@8E<0;8
D0:B>@8 @878:C 70AB>N C 6>2G>282V4=8E H;OE0E, =0?@8:;04, ;V:C20==O 2 0=0<=57V, BO6:V
70E2>@N20==O B0 ?>2=VABN ?0@5=B5@0;L=5 E0@GC20==O.
@8 FL>
I>:C 35?0B>1V;V0@=>W A8AB5<8: 71V;LH5==O :V;L:>ABV D5@<5=BV2 ?5GV=:8 C A8@>20BFV
:@>2V (!", ", ;C6=0 D>AD0B070), O45@=0 6>2BO=8FO. !?>AB5@V30;0AO ?@5F8?VB0FVO
F5DB@80:A>=C :0;LFTV2>W A>;V C 6>2G=>B@870<8, I> ?5@528ICNBL @5:><5=4>20=C
AB0=40@B=C 4>7C. # 4VB59 C ?@>A?5:B82=8E 4>A;V465==OE ?@8 2=CB@VH=L>25==>AC20==V
?@5?0@0BC A?>AB5@V30;0AO @V7=0 G0AB>B0 CB2>@5==O ?@5F8?VB0BC, C 450:8E
4>A;V465==OE ?>=04 30 %. '0AB>B0 CB2>@5==O ?@5F8?VB0BC <5=H0 ?@8 ?@>2545==V
?>2V;L=>W V=DC7VW
(20-30 E28;8=). &59 5D5:B, O: ?@028;>; 0A8<0B8G=89, 0;5 C @V4:VA=8E 28?04:0E ?@5F8?VB0FVO
AC?@>2>46CTBLAO B0:8<8 ;;V=VG=8<8 A8<0<8 O: 1V;L, =C4>B0 V 1;N20==O. # F8E 28?04:0E @5:>
<5=4>20=5 A8<0B8G=5 ;V:C20==O. @5F8?VB0FVO, O: ?@028;>;, T >1>@>B=>N ?VA;O ?@8?8=5==O
70AB>AC20==O F5DB@80:A>=C.
I>:C H:V@8 B0 ?V4H:V@=>W ;;VB:>28=8: 0;5@3VG=V H:V@=V @50:FVW, B0:V O: 28A8?0==O, C
B.G. <0:C;>?0?C;L>7=V, :@>?82'O=:0, 0;5@3VG=89 45@<0B8B, A25@1V6, =01@O:. C;LB8D>@<=0
5@8B5<0, A8=4@< !BV25=A0-6>=A>=0, A8=4@< 09T;;0/B>:A8G=89 5?V45@<0;L=89 =5:@>;V7,
3>AB@89 35=5@0;V7>20=89 5:75<0B>7=89 ?CABC;L>7.
I>:C A5G>284V;L=>W A8AB5<8: >;V3C@VO, 3;N:>7C@VO, 35<0BC@VO. @5F8?VB0B C =8@:0E,
?5@5206=> C 4VB59 2V:< 2V4 3 @>:V2, O:8E ;V:C20;8 =0928I8<8 4>1>28<8 4>70<8 (80 <3:/3/4>1C V
1V;LH5) 01> 7030;L=8<8 4>70<8, I> ?5@528ICNBL 10 3, 0 B0:>6 7 V=H8<8 D0:B>@0<8 @878:C, B0:8<8
O: 453V4@0B0FVO 01> V<>1V;V70FVO. #B2>@5==O ?@5F8?VB0BC C =8@:0E T >1>@>B=8< ?VA;O
?@8?8=5==O 70AB>AC20==O F5DB@80:A>=C. # 72'O7:C 7 F8< ?>2V4<<;O;>AO ?@> 0=C@VN V
?>@CH5==O DC=:FVW =8@>:.
030;L=V ?>@CH5==O: >7=>1, ?V@5:AVO.
50:FVW C <>65 @>72820B8AO D;51VB V 1V;L C?@>BO3< ?@8=09<=V 2-4 E28;8=. =CB@VH=L>
<O7>20 V='T:FVO 157 70AB>AC20==O ;V4>:0W=C T 1>;VA=>N.
?;82 =0 @57C;LB0B8 ;01>@0B>@=8E ?>:07=8:V2: ?V428I5==O @V2=O :@50B8=V=C 2 :@>2V,
E81=>?>78B82=89 B5AB C<1A0. /: V V=HV 0=B81V>B8:8, F5DB@80:A>=<>65 A?@8G8=OB8
E81=>?>78B82=89 @57C;LB0B ?@>18 =0 30;0:B>75?>78B82=V @57C;LB0B8 <>6CBL 1CB8 >B@8<0=V
V ?@8 287=0G5=V 3;N:>78 2 A5GV, B=>7C@VN, C @07V =5>1EV4=>ABV, A;V4287=0G0B8 ;8H5 D5@
<5=B=8< <5B>4>
70T<>4VO 7 :0;LFVT
V4:VA=V 28?04:8 BO6:8E =51060=8E @50:FV9, V=>4V V7 ;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;LFTV. @8 0CB>?AVW C ;535=OE B0 =8@:0E 1C;8 28O2;5=V
?@5F8?VB0B8 :0;LFTV2>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 (482. @>74V;8 «@>B8?>:070==O», «A>1;82>ABV 70AB>AC20==O»).

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@8 25;8:V 4>1>2V 4>78 ?@5?0@0BC (=0?@8::;04 ≥ 80 <3/:3/4>1C) 01> 7030;L=V 4>78 ?>=04

10 3@06 <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 (482. @>74V;«A>1;82>ABV 70AB>AC20==O»).

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 A&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 (482. @>74V;«A>1;82>ABV 70AB>AC20==O»).

5@54>7C20==O.

!8<8: <>6;82V ?@>?0A=8FO, ;59:>?5=VO, B@<1>F8B>?5=VO, 3>AB@0 35<>;VB8G=0 0=52>-:8H:>2V @50:FVW B0 @50:FVW ?5GV=:8, 7048H:0, =8@:>20 =54>AB0B=VABL, AB<0B8B, 0=>@5:AVO, B820 2B@0B0 A;CEC, 2B@0B0 >@VT=B0FVW C ?@>AB>@V. V:C20==O: ?@>2>4OBL A8<0B8G=C V ?V4B@83> 0=B84>BC =5<0T. 5<>4V0;V7 V ?5@8B>=50;L=89 4V0;V7 =55D5:B82=V.

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=8< 6V=:0A;V465==O =0 B20@8=0E =5 A2V4G0BL ?@> 157?>A5@54=V9 01> >?>A5@54:>20=89 H:V4;8289 2?;82 =0 5<1@V>=/?;V4, ?5@8- B0 ?>AB=0B0;L=89 @>728B>:. V4 G0A 203VB=>ABV, 7>:@5<0 C ?5@H> >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> 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.

VB8.

@5?0@0B 70AB>A>2CNBL 4VBO< 73V4=> 7 4>7C20==O<, 707=0G5=8< C @>74V;V «!>AV1 70AB>AC20==O B0 4>78».

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

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

!/: V ?@8 70AB>AC20==V 2AVE 15B0-;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 (482. @>74V; «>1VG=V @50:FVW»). # 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 15B0-;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 15B0-;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 (482.
@>74V; <>1VG=V @50:FVW»).

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> 703> ?@><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 F5DB@80: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.

@5?0@0B ?@>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 (482. @>74V; <>@>B8?>:070==O)).
>?>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=V2, O:V >B@818 :;0AC
F5D0;>A?>@8=V2 (482. @>74V; <>1VG=V @50:FVW»). "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=5
FV9>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.
&5DB@80:A>= <>65 71V;LHC20B8 ?@>B@<1V=>289 G0A. # 72'O7:C 7 F8< ?@8 ?V4>7@V =0
45DVF8B 2VB01EV4=> 287=0G0B8 ?@>B@<1V=>289 G0A.
>;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 D=>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=V2, C O:8E ?V4
G0A 01> ?VA;O 70AB>AC20==O F5DB@80:A>=C 28=8:;0 4V0@50 (482. @>74V; <>1VG=V @50:FVW»).
!;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 (5=B5@>:>:8 V HB0<8 *Candida*).
&5DB@80:A>= ?>B@V1=> 7 >15@56=VABN 70AB>A>2C20B8 ?0FVT=B0< V7 :8H:>2>-H;C=>28<8
70E2>@N20==O<8 2 0=0<=57V, 7>:@5<0 :>;VB>

"06:0=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 (482. @>74V; «!>AV1
70AB>AC20==O B0 4>78»). !;V4 28O2;OB8 >15@56=VABL ?@8 70AB>AC20==V F5DB@80:A>=C E2>@8
< V7 =8@:>2>N =54>AB0B=VABN, O:V >4=>G0A=> >B@83;V:>7848 B0 4VC@5B8:8.
?;82 =0 @57C;LB0B8 A5@>;>3VG=8E 4>A;V465=L.

@8 70AB>AC20==V F5DB@80:A>=C B5AB C<1A0 <>65 4020B8 E81=>?>78B82=V @57C;LB0B8. "0:>6
?@5?0@0B <>65 A?@8G8=OB8 E81=>?>78B82=V @57C;LB0B8 0=0;V7C =0 =0O2=VABL 30;0:B>7574V;
<>1VG=V @50:FVW»).

@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 F5DB@80: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 (482. @>74V; <>1VG=V @50:FVW»).

OB@V9.
>65= 3@0< ?@5?0@0BC =B@>;L>20=8< 2< =0B@VN.

!75: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 (482. @>74V; «!>AV1 70AB>AC20==O B0 4>78»). # 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:FVW 4;O <548G=>3> 70AB>AC20==O ;V4>:0W=C (482. @>74V; «@>B8?>:070==O»). @8
2=CB@VH=L<<'O7>28E V='T:FVOE >4@07C 6 ?VA;O C:>;C @5:><5=4CTBLAO 28BO3=CB8 ?>@H5=L
H?@8F0 (=5 ?>28==0 7'O2;OB8AO :@>2), I>1 ?5@5:>=0B8AO, I> 3>;:0 =5 ?>B@0?8;0 C :@>2>=>A=C
AC48=C. !;V4 28:>@8AB>AC20B8 A2V6>?@83>B>2;5=V @>7G8=8.

>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 3/4>1C B0 28I5. A>1;82>W >15@56=>ABV A;V4 4>B@8AC20==V
?@5?0@0BC 4VBO□VBO< =5 A;V4 70AB>A>2C20B8 4>78, I> ?5@528ICNBL 80 <3/:3 <O A8 BV;0,
>A:V;L:8 ?V428ICTBLAO @878: CB2>@5==O 6>2G=>3> ?@5F8?VB0BC. "0:V ?@5F8?VB0B8 7=8:0NBL
?VA;O ?@8?8=5==O B5@0?VW F5DB@80:A>=>@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 (482.
@>74V; <>1VG=V @50:FVW»).

>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= (482. @>74V; <>1VG=V @50:FVW»). 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 F5DB@80: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 (482. @>74V; <>1VG=V @50:FVW»). # 28?04:C =0O2=>ABV A818B8
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 C :>6=>=:@5B=>

40B=VABL ??;820B8 =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B< 01> @>1>BV 7
V=H8<8 <5E0=V7<0<8.

V4?>2V4=V 4>A;V465==O =5 ?@>2>48;8AO. # 7207:C 7 <>6;82VABN 28=8:=5==O B0:8E ?>1VG=8E @50:FV9, O: 70?0<>@>G5==O, F5DB@80:A>= <>65 2?;820B8 =0 740B=VABL :5@C20B8 B@0=A?>@B=8 <8 70A>10<8 01> ?@0FN20B8 7V A.;04=8<8 <5E0=V7<0<8.

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

>7G8==8:8, I> , B0:V O: @>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 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 &5DB@80:A>= =5 <>6=0 22>48B8 >4=>G0A=> V7 @>7G8=0<8 4;O 2=CB@VH=L>25==>3> 22545==O, I> T2Y-?>4V1=>W A8AB5<8. 4=0: @5HBV ?0FVT=BV2, :@V< =>2>=0@>465=8E, F5DB@80:A>= B0 :0;LFV T27G8=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 (482. @>74V;8 <!>AV1 70AB>AC20==O B0 4>78», «@>B8?>:070==O», «A>1;82>ABV 70AB>AC20==O», «>1VG=V @50:FVW»).

3;V:>7848. A=CNBL AC?5@5G;82V 40=V I>4> ?>B5=FV9=>3> ?>A8;5==O B>:A8G=>3> 2?;82C 0 3;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.

5AB5@>W4=V ?@>B870?0;L=V 70A>18, 0=B803@530=B8, 0=B03>=VAB8 2VB0(=0?@8:;04, 20@D0@8=): ?V428I5==O <>6;82>ABV :@>2>B5GV.

!C5 70AB>AC20==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=>< (482. @>74V; <>1VG=V @50:FVW»).

5B;L>2V 4VC@5B8:8 B0 =5D@>B>:A8G=V ?@5?0@0B8 - ?V428ICTBLAO @878: =5D@>B>:A8G=>ABV.

0:B5@V>AB0B8G=V 0=B81V>B8:8 (E;>@0;, B5B@0F8:;V=8): 7=86CNBL 10:B5@8F84=89 5D5:B F5DB@80:A>=C. # 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.

>@<>=0;L=V :>=B@0F5?B828: 7=86CTBLAO 5D5:B82=VABL 3>@<>=0;L=8E :>=B@0F5?B82V2, B> <5=4CTBLAO 28:>@8AB>2C20B8 4>40B:>2V (=53>@<>=0;L=V) <5B>48 :>=B@0F5?FVW ?V4 G0A ;V:C20==O B0 ?@>B03< 1 3> 7025@H5==O.

=HV 15B0-;0:B0<=V 0=B81V>B8:8: <>6;82VABL @>728B:C ?5@5E@5A=8E 0;5@3VG=8E @50:FV9. VA;O 70AB>AC20==O 5B0=>;C>4@07C ?VA;O ?@89>C =5 A?>AB5@V30;>AO 5D5:BV2, AE>68E =0 4VN 48AC;LDV@0

&5DB@80:A>= =5 N-<5B8;BV>B5B@07>;L=C 3@C?C, O:0 1 <>3;0 ?@825AB8 4> =5?5@5=>A8<>ABV 5B0=>;C 01> :@>2>B5GV, I> 2;0AB82> 450:8< V=H8< F5D0;>A?>@8=0

@>15=5F84: =5 2?;820T =0 :0=0;LF52C A5:@5FVN F5DB@80:A>=C (=0 2V4A?>@8=V2).

/: V V=HV 0=B81V>B8:8, F5DB@80:A>= <>65 7=86C20B8 B5@0?52B8G=89 5D5:B 20:F8=8 ?@>B8 B8DC , ?@>B5 B0:89 5D5:B @>7?>2AN46CTBLAO ;8H5 =0 >A;01;5=89 HB0< Ty21.

>7G8= &5DB@80:A>=C-0@=8FO =5 A;V4 7 22>48B8 >4=>G0A=> 7 V=H8<8 0=B81=8<8 ?@5?0@0B0<8 C 72?07:C 7 D0@<0F52B8G=>N =5AC

&5DB@80:A>= =5ACV 9>3> =5 <>6=0 77 0<70:@8=><, 20=:><, D;C:>=07>;>< B0 03;V:>7840<8.

\$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.

V:@>1V>;>3VO. 0:B5@8F84=0 0:B82=VABL F5DB@80:A>=C 7C<>2;5=0 ?@83=VG5==O< A8=B57C
 ;;VB8==8E <5<1@0=. &5DB@80:A>= 0:B82=89 in vitro 2V4=>A=> 1V;LH>ABV 3@0<=530B82=8E V 3@0
 78B82=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>=
 0:B82=89 2V4=>A=> B0:8E >@30=V7in vitro V ?@8 ;V=VG=8E V=D5:FVOE (482. @>74V; <>:070==O»):
 @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. !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 28O2;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, *Capnocytophagaspp.*, *Citrobacter diversus* (2 B>C. *amalonaticus*), *Citrobacter freundii**, *Escherichia*
coli, *Enterobacter aerogene**, *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 gonorrhoea*5, *Neisseria meningitidis*, *Pasteurella multocida*,
Plesiomonas shigelloides, *Proteus mirabilis*, *Proteus penner**, *Proteus vulgaris**, *Pseudomonas fluorescens**,
Pseudomonas spp. (V=HV)*, *Providentia rettger**, *Providentia spp.* (V=HV), *Salmonella typhi*, *Salmonella spp.*
 (=5B8D>W4=V), *Serratia marcescens**, *Serratia spp.* (V=HV)*, *Shigella spp.*, *Vibrio spp.*, *Yersinia enterocolitica*,
Yersinia spp. (V=HV).

* 5O: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.

** 5O:V V7>;OB8 F8E 284V2 ABV9:V 4> F5DB@80:A>=C C=0A;V4>: CB2>@5==O =87:8 ?;07-
 >?>A5@54:>20=8E β-;0:B0<07.

030B> 7V 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 ?5@H>3> B0 4@C3>3> ?>:>;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 V C 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> V 2B>@8==>3>
 A8DV;VAC, 70 28=OB:× ;V=VG=8E HB0P. *Aeruginosa*, ABV9:8E 4> F5DB@80:A>=C.

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

* 5O:V V7>;OB8 F8E 284V2 ABV9:V 4> F5DB@80:A>=C 2=0A;V4>: CB2>@5==O β-;0:B0<07.

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:

"01;8FO 1.

	'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>=><, >A:V;L:8 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.

0! 4;O 287=0G5==O GCB;82>ABV >@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, 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 >4=>@07>2>3> 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 ?@5?0@0BC ?@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@0FVW 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 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, <8340;8:0E, 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).

VA;O 2=CB@VH=L>25==>3> 22545==O F5DB@80:A>= H284:> ?@=>8:0T C A?8==>>7:>2C @V48=C, 45 10:B5@8F84=V :=F5=B@0FVW I>4> GCB;828E >@30=V7BO3<< 24 3>48=.

2'O7C20==O 7 IV;:0<8. &5DB@80:A>=>1>@>B=> 72'O7CTBLAO 7 0;L1C<, ?@8G>2V <5=H5 100 <3/; 4> 85 % ?@8 :=F5=B@0FVW 300 <3/;. 0240:8 =86GV9 :=F5=B@0FVW 0;L1C3> F5DB@80:A>=C C =V9 28I0, =V6 C ?;072V.

@>=8:=5==O 2 >:@5&5DB@80:A>= ?@>=8:0T G5@57 70?0;5=V <>7:>2V >1>;>=8 C 4VB59, C B.G. =>2>=0@>465=8E. '5@57 24 3>48=8 ?VA;O 2=CB@VH=L>25==>3> 22545==O F5DB@80:A>=C C 4>7V

50-100 <3/:3 <0A8 BV;0 (=2>=0@>465=8< B0 =5<>2;OB0< 2V4?>2V4=>) :=F5=B@0FVW F5DB@80:A>=C C A?8==>>7:>2V9 @V48=V ?5@528ICNBL 1,4 <3/;. 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 %. # 4>@>A;8E E2>@8E =0 <5=V=3VB ?VA;O 22545==O 4>78 50 <3/:3 <0A8 BV;0 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 C 1030B> @07V2 ?5@528ICNBL

&5DB@80:A>= ?@>E>48BL G5@57 ?;0F5=B0@=89 10@'T@ B0 C <0;8E :=F5=B@0FVOE 284V;OTBLAO C 3@C4=5 <>;>.

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 AB0=>28BL 10-22<;/E2. 8@:>289 ;;V@5=A AB0=>28BL 5-12 <;/E2. 50-60 % F5DB@80:A>=C 282>48BLAO C =57 283;04V =8@:0<8 V 40-50 % 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>1;828E ;;V=VG=8E 28?04:0E. # =>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=V2 AB0@H5 75 @>:V2 ?5@V>4 =0?V2282545==O C A5@54=L> # E2>@8E V7 =8@:>2>N 01> ?5GV=:>2>N =54>AB0B=VABND0@<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. /: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.

\$0@<0F52B8G=V E0@0:B5@8AB8:8.

A=>2=V DV78:>-EVABV: :@8AB0;VG=89 ?>@>H:> <0965 1V;>3> 01> 1V;>3> 7 6>2BC20B8< 2V4BV=:>< :>;L>@C, A;01> 3V3@>A:>?VG=89.

5AC

&5DB@80:A>=-0@=8FO =5 <>6=0 7

&5DB@80:A>= =5AC<, 20=:><, D;C:>=07>;< B0 03;V:>7840<8.

5 A;V4 7

"5@ABV.3 @>:8.

#<>28 715@V30==O. 15@V30B8 2 >@83V=0;L=V9 C?0:>2FV C =54>ABC?=>

#?0:>2:0.

> 0,5 3 01> 1 3 ?>@>H:C C D;0:>=V; ?> 1, 5 01> 40 D;0:>=V2 2 C?0:>2FV. > 1 D;0:>=C ?> 0,5 3 ?>@>H:C
B0 1 0 @>7G8==8:0 (>40 4;O V='T:FV9-0@=8FO 2 0 5 <); 2 C?0:>2FV. >1 D;0:>=C ?> 1 3 ?>@>H:C
B0 1 0 @>7G8==8:0 (>40 4;O V='T:FV9-0@=8FO 2 0 ?> 10 <); 2 C?0:>2FV.

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

8@>1=8:.

@ " «\$0@<0F52B8G=0 DV@<0 «0@=8FO».

VAF57=0E>465==O.

#:@0W=0, 02093, @8A?i;LAL:0, 13.

!" #&/
> <548F8=A:>

&\$" !-&
(CEFTRIAZONE-DARNITSA)

!>AB02:

459AB2CNI55 25I5AB2>: ceftriaxone;

1 D;0:>= A>45@68B F5DB@80:A>=0 =0B@852>9 A>;8 2 ?5@5AG5B5 =0 F5DB@80:A>= 500 <3 (0,5 3) 8;8
1 3.

5:0@AB25==0O D>@<0. >@>H>: 4;O @0AB2>@0 4;O 8=J5:F89.

\$0@<0:>B5@0?52B8G5A:0O 3@C??0. =B810:B5@80;L=K5 A@54AB20 4;O A8AB5<=>3> ?@8<5=5=8O.
@C385 15B0-;0:B0<=K5 0=B818>B8:8. ?>A?>@8=K III ?>:>;5=8O. &5DB@80:A>=
>4 " ! J01D D04.

;8=8G5A:85 E0@0:B5@8AB8:8.

>:070=8O.

&5DB@80:A>=- □ 0@=8F0 ?@8<5=OBL 4;O ;5G5=8O 8=D5:F89, 2>71C48B5;8 :>B>@KE
GC2AB28B5;L=K : F5DB@80:A>=C:

□ 8=D5:F88 4KE0B5;L=KE ?CB59, >A>15==> ?=52<>=8O, 0 B0:65 8=D5:F88 CE0, 3>@;0 8 =>A0;

□ 8=D5:F88 >@30=>2 1@NH=>9 ?>;>AB8 (?5@8B>=8B, 8=D5:F88 65;G52K2>4OI8E ?CB59 8
65;C4>G=>:-:8H5G=>3> B@0:B0);

□ 8=D5:F88 ?>G5: 8 <>G52K2>4OI8E ?CB59;

□ 8=D5:F88 ?>;>2KE >@30=>2, 2;NG00 3>=>@5N;

□ A5?A8A;

□ 8=D5:F88 :>AB59, ACAB02>2, 68, 0 B0:65 @0=52K5 8=D5:F88;

□ 8=D5:F88 C 1>;L=KE A >A;01;5==>9 8<9 70I8B>9;

□ <5=8=38B;

□ 48AA5<8=8@>20==K9 1>@>5;8>7 09<0 (AB0488 II 8 III).

5@8>?5@0F8>==0O ?@>D8;0:B8:0 8=D5:F89 ?@8 E8@C@38G5A:8E 2<5H0B5;LAB20E =0 >@30=0E
65;C4>G=>:-:8H5G=>3> B@0:B0, 65;G52K2>4OI8E ?CB59, <>G52K2>4OI8E ?CB59 8 2> 2@5;>38G5A:8E
?@>F54C@, => B>;L:> 2 A;CG0OE ?>B5=F80;L=>9 8;8 8725AB=>9 :>=B0<8=0F88.

@8 =07=0G5=88 ?@5?0@0B0 =5>1E>48<> ?@845@6820BLAO >D8F80;L=KE @5:>5=40F89 ?> 0=B818>B8:>B5@0?88 8, 2 G0AB=>AB8, @5:>5=40F89 ?> ?@>D8;0:B8:5 0=B818>B8:>@578AB5=B=>AB8.

@>B82>?>:070=80.

>2KH5==0O GC2AB28B5;L=>ABL : F5DB@80:A>=C 8;8 ;N1>A?>@8=C. 0;8G85 2 0=0<=575 BO65;KE @50:F89 38?5@GC2AB28B5;L=>AB8 (=0?@8<5@, 0=0D8;0:B8G5A:8E @50:F89) : ;N1>

&5DB@80:A>= ?@>B82>?>:070=:

54=>=>H5==K< =>2>@>645==K< 2 2>7@0AB5 ≤ 41 =545;O A CG5B< A@>:0 2=CB@8CB@>1=>3> @0728B8O (35AB0F8>==K9 2>7@0AB + 2>7@0AB ?>A;5 @>645=8O). 8AA;54>20=8OE *in vitro* 1K;> ?>:070=>, GB> F5DB@80:A>= <>65B 2KB5A=OBL 18;8@C18= 87 A2O78 A 0;L1C<8=>< AK2>@>B:8 :@>28, GB> ?@82>48B : 2>7<>6=>2>9 M=F5D0;>?0B88 C B0:8E ?0F85=B>2.

>=>H5==K< =>2>@>645==K< (2 2>7@0AB5 ≤ 28 4=59):

- A 38?5@18;8@C18=5<859, 65;BCE>9, 38?>0;L1C<8=5<859 8;8 0F84>7<, ?>A:>;L:C ?@8 B0:8E A>AB>O=8OE A2O7K20=85 18;8@C18=0, 25@>OB=>, =0@CH5=>.
- :>B>@K5 B@51CNB (8;8 >68405BAO, GB> 1C4CB B@51>20BL) 22545=8O ?@5?0@0B>2 :0;LF8O 8;8 8=DC789 :0;LF89A>45@60I8E @0AB2>@>2, ?>A:>;L:C ACI5AB2C5B @8A: >1@07>20=8O ?@5F8?8B0B>2 :0;LF852>9 A>;8 F5DB@80:A>=0 (A15==>AB8 ?@8<5=5=8O) 8 «>1>G=K5 @50:F88»). 5@54 2=CB@815==>AB8 ?@8<5=5=8O). ! ?@8<5=5=8N ;84>:08=0, >A>15==> ?@>B82>?>:070=8O. 0AB2>@K F5DB@80:A>=0, A>45@60I85 ;84>:08=, =8:>340 =5 A;54C5B 22>48BL 2=CB@825==>.

!>A>1 ?@8<5=5=8O 8 4>7K.

7@>A;K5 8 45B8 2 2>7@0AB5 AB0@H5 12 ;5B: =07=0G0BL 1-2 3 F5DB@80:A>=0 1 @07 2 ACB:8 (:064K5

24 G0A0). @8 BO65;KE 8=D5:F8OE 8;8 8=D5:F8OE, 2>71C48B5;8 :>B>@KE 8<5NB ;8HL C<5@5==CN GC2AB28B5;L=>ABL : F5DB@80:A>=C, ACB>G=CN 4>7C <>6=> C25;8G820BL 4> 4 3.

>2>@>645==K5, <;045=FK 8 45B8 2 2>7@0AB5 4> 12 ;5B.

865 ?@82>4OBAO @5:>5=4C57K 4;O ?@8<5=5=8O 1 @07 2 ACB:8.

>2>@>645==K5 4> 2 =545;L: 20-50 <3/:3 <0AAK B5;0 1 @07 2 ACB:8, ACB>G=0O 4>70 =5 4>;6=0 ?@52KH0BL 50 <3/:3 <0AAK B5;0. @8 ?>@545;5=88 4>7K ?@5?0@0B0 4;O 4>=>H5==KE 8 =54>=>H5==KE 45B59 >B;8G89 =5B.

&5DB@80:A>= ?@>B82>?>:070= =>2>@>645==K< 2 2>7@0AB5 ≤ 28 4=59 ?@8 =5>1E>48<>AB8 (8;8 >68405<>9 =5>1E>48<>AB8) ;5G5=8O 2=CB@825==K<8 @0AB2>@0<8, A>45@60I8<8 :0;LF89, 2 B<< G8A;5 ?>AB>O==K5 2=CB@825==K5 2;820=8O, :>B>@K5 A>45@60B :0;LF89, =0?@8<5@, ?0@5=B5@0;L=>5 ?8B0=85, 2 A2O78 A @8A:> 2>7=8=>25=8O ?@5F8?8B0B>2 :0;LF852KE A>;59 F5DB@80:A>=0 (AB82>?>:070=8O)).

>2>@>645==K5 8 45B8 2 2>7@0AB5 4> 12 ;5B: 20-80 <3/:3 <0AAK B5;0 1 @07 2 ACB:8.

5BO <A <0AA>9 B5;0 1>;55 50 :3 =07=0G0BL 4>7K 4;O 27@>A;KE.

=CB@825==K5 4>7K 50 <3/:3 8;8 2KH5 A;54C5B 22>48BL ?CB5< 8=DC788 2 B5G5=85 ?> :@09=59 <5@5

30 <8=CB. >7K, ?@52KH0NI85 80 <3/:3 <0AAK B5;0, =5 A;54C5B ?@8<5=OBL 87-70 ?>2KH5==>3> @8A:0 65;G=>9 ?@5F8?8B0F88.

0F85=BK ?>68;>3> 2>7@0AB0.

;O ?0F85=B>2 ?>68;>3> 2>7@0AB0, ?@8 CA;>288 =04;560I53> DC=:F8>=8@>20=8O ?>G5: 8 ?5G5=8, :>@>5:F8O 4>7K =5 B@51C5BAO.

@>4>;68B5;L=>ABL ;5G5=8O.

>7C 8 A?>A>1 ?@8<5=5=8O A;54C5B >?@545;OBL 2 7028A8<>AB8 >B BO65AB8 8=D5:F88, GC2AB28B5;L=>AB8 ?0B>35==>3> <8:@>>@30=87<0 8 A>AB>O=8O ?0F85=B0. 1>;LH8=AB25 A;CG052 C4>2;5B2>@8B5;L=K5 B5@0?52B8G5A:85 @57C;LB0BK <>3CB 1KBL ?>;CG5=K ?@8 ?@8<5=5=88 ?@5?0@0B0

1 @07 2 ACB:8.

@>4>;68B5;L=>ABL B5@0?88 7028A8B >B B5G5=8O 701>;520=8O. 0: ?@8=OB> ?@8 B5@0?88

0=B818>B8:0<8, ?@8<5=5=85 ?@5?0@0B0 &5DB@80:A>= A;54C5B ?@>4>;60BL <8=8 2 B5G5=85

48-72 G0A>2 ?>A;5 8AG57=>25=8O C ?0F85=B0 ;8E>@04:8 8;8 ?>A;5 ?>;CG5=8O @57C;LB0B0, GB> A2845B5;LAB2C5B > 10:B5@80;L=>9 M@048:0F88.

><18=8@>20==0O B5@0?8O.

AA;54>20=8O ?>:070;8, GB> 2 >B=>H5=88 <=>38E 3@0<>B@8F0B5;L=KE 10:B5@89 ACI5AB2C5B A8=5@387< <564C F5DB@80:A>=>< 8 0<8=>3;8:>7840<8. 5A<>B@O =0 B>, GB> ?>2KH5==CN MDD5:B82=>ABL B0:8E :<18=0F89 =5 2A5340 <>6=> ?@54CA<>B@5BL, 55 A;54C5B 8<5BL 2 284C ?@8 =0;8G88 BO65;KE, C3@>60NI8E 687=8 8=D5:F89, 2K720==KE *Pseudomonas aeruginosa*. 7-70 D878G5A:>9 =5A>2<5AB8<>AB8 F5DB@80:A>=0 8 0<8=>3;8:>784>2 8E A;54C5B 22>48BL >B45;L=> 2 @5:><5=4>20==KE 4>70E.

>78@>20=85 2 >A>IKE A;CG0OE.

5=8=38B.

@8 10:B5@80;L=>< <5=8=38B5 C <;045=F52 8 45B59 2 2>7@0AB5 4> 12 ;5B ;5G5=85 =0G8=0BL A 4>7K

100 <3/:3 (=> =5 1>;55 4 3) 1 @07 2 ACB:8. 0: B>;L:> 2>71C48B5;L 1C45B 845=B8D8F8@>20=, 0 53>

GC2AB28B5;L=>AB8 >?@545;5=0, 4>7C <>6=> A>>B25BAB25==> C<5=LH8BL. 08;CGH85

@57C;LB0BK 4>AB830;8AL ?@8 B0:>9 ?@>4>;68B5;L=>AB8 ;5G5=8O:

<i>Neisseria meningitidis</i>	4 4=O
<i>Haemophilus influenzae</i>	6 4=59
<i>Streptococcus pneumoniae</i>	7 4=59

>@@5;8>7 09<0: 27@>A;K< 8 45BO< 50 <3/:3 (2KAH0O ACB>G=0O 4>70 2 3) 1 @07 2 ACB:8 2 B5G5=85 14 4=59.

>=>@5O.

;O ;5G5=8O 3>=>@58 (2K720==>9 >1@07CNI8<8 8 =5 >1@07CNI8<8 ?5=8F8;;8=07C HB0<<0<8) @5:> <5=4C5BAO =07=0G0BL @07>2CN 4>7C 250 <3 2=CB@8.

@>D8;0:B8:0 8=D5:F89 2 E8@C@388.

;O ?@>D8;0:B8:8 ?>A;5>?5@0F8>==KE 8=D5:F89 ?@8 :=B0<8=8@>20==KE 8;8 ?>B5=F80;L=> :=B0 <8=8@>20==KE E8@C@38G5A:8E 2<5H0B5;LAB20E @5:><5=4C5BAO 2 7028A8<>AB8 >B AB5?5=8 >?0A=>AB8 70@065=8O 22>48BL @07>2CN 4>7C 1-2 3 F5DB@80:A>=0 70 30-90 <8=CB 4> =0G0;0 >?5@0F88. @8 >?5@0F8OE =0 B>;AB>9 8 ?@O<>9 :8H:5 E>@>H> 70@5:><5=4>20;> A51O >4=>2@5 <5==>5 22545=85 F5DB@80:A>=0 8 >4=>3> 87 5=-8B@>8<8407>;>2, =0?@8<5@, >@=8407>;0.

0@CH5=85 DC=:F88 ?>G5: 8 ?5G5=8.

1>;L=KE A =0@CH5=8O<8 DC=:F88 ?>G5: =5B =5>1E>48<>AB8 C<5=LH0BL 4>7C, 5A;8 DC=:F8O ?5G5=8 >AB05BAO =>@<0;L=>9. ">;L:> 2 A;CG05 ?>G5G=>9 =54>AB0B>G=>AB8 2 ?5@54B5@<8=0;L=> >9 AB0488 (:;8@5=A :@50B8=8=0 <5=55 10 <;<8=) ACB>G=0O 4>70 =5 4>;6=0 ?@52KH0BL 2 3.

>;L=K<, =0E>4OI8480;875, =5B =5>1E>48<>AB8 2 4>?>;=8B5;L=>< 22545=88 ?@5?0@0B0 ?>A;5 480;870. !;54C5B >4=0: >:=B@>;8@>20BL :=F5=B@0F8N F5DB@80:A>=0 2 AK2>@>B:5 :@>28, ?>A;>;L:C C MB8E 1>;L=KE <>65B A=860BLAO A:>@>ABL 2K2545=8O. !CB>G=0O 4>70 ?@5?0@0B0 C 1>;L=KE, =0E>4OI8EAO =0 480;875, =5 4>;6=0 ?@52KH0BL 2 3.

1>;L=KE A =0@CH5=8O<8 DC=:F89 ?5G5=8 =5B =5>1E>48<>AB8 C<5=LH0BL 4>7C, 5A;8 DC=:F8O ?>G5: >AB05BAO =>@<0;L=>9.

@8 >4=>2@5<5==>< BO65;>< =0@CH5=88 DC=:F88 ?>G5: 8 ?5G5=8 A;54C5B @53C;O@=>

>?@545;OBL :=F5=B@0F8N F5DB@80:A>=0 2 ?;07<5 :@>28 8 ?@>2>48BL :=@>@5:F8N 4>7K ?@5?0@0B0 2 A;CG05 =5>1E>48<>AB8, ?>A;>;L:C C@>25=L 2K2545=8O C B0:8E ?0F85=B>2 <>65B A=860BLAO.

@83>B>2;5=85 @0AB2>@>2.

>AAB0=>2;5==K5 @0AB2>@K A;54C5B 8A?>;L7>20BL A@07C ?>A;5 ?@83>B>2;5=8O.

=CB@8

;O 8=J5:F88 1 3 @0AB2>@OBL 2 3,5 <; 1 % @0AB2>@0 ;84>:08=0; 8=J5:F8N 45;0BL 2 F5=B@ 1>;LH>9 48BL =5 1>;55 1 3 2 >48= CG0AB>:.

A;8 ;84>:08= ?@8<5=ONB 2 :0G5AB25 @0AB2>@8B5;O, ?>;CG5==K9 @0AB2>@ =8:>340 =5 A;54C5B 22>48BL 2=CB@825==> (A<. @0745; «@>B82>?>:070=8O»). ;O 45B0;L=>9 8=D>@<0F88 =5>1E>48<> >7=0:><8BLAO A 8=AB@C:F859 ?> ?@8<5=5=8N ;84>:08=0.

@8<5=5=85 ;84>:08=0 ?@54CA<0B@8205B ?@5420@8B5;L=>5 ?@>2545=85 ?@>1K 4;O ?>@545;5=8O
8=48284C0;L=>9 GC2AB28B5;L=>AB8 : MB>
=CB@825==0O 8=J5:F8O.
;O 2=CB@825==>9 8=J5:F88 A;54C5B @0AB2>@8BL 1 3 F5DB@80:A>=0 2 10 <; 2>4K 4;O 8=J5:F89;
22>48BL 2=CB@825==> <54;5==> (2-4 <8=CBK).
=CB@825==0O 8=DC78O.

=CB@825==>5 2;820=85 4>;6=> 4;8BLAO =5 <5=55 30 <8=CB. ;O ?@83>B>2;5=8O @0AB2>@0 4;O
2;820=8O @0AB2>@8BL 2 3 ?@5?0@0B0 2 40 <; >4=>3> 87 A;54CNI8E 8=DC78>==KE @0AB2>@>2,
A2>1>4=KE >B 8>=>2 :0;LF8O: 0,9 % E;>@84 =0B@8O, 0,45 % E;>@84 =0B@8O + 2,5 % 3;N:>70, 5 %
3;N:>70, 10 % 3;N:>70, 6 % 45:AB@0= 2 @0AB2>@5 3;N:>7K 5 %, 6-10 % 384@>:A8MB8;8@>20==K9
:@0E<0;, 2>40 4;O 8=J5:F89. #G8BK20O 2>7<>6=CN =5A>2<5AB8<>ABL, @0AB2>@K, A>45@60I85
F5DB@80:A>=, =5;L7O A<5H820BL A @0AB2>@0<8, A>45@60I8<8 4@C385 0=B818>B8:8, :0: ?@8
?@83>B>2;5=88, B0: 8 ?@8 22545=88.

4=0:> 2 3 F5DB@80:A>=0 8 1 3 >@=8407>;0 D878G5A:8 8 E8<8G5A:8 A>2<5AB8
5;L7O 8A?>;L7>20BL @0AB2>@8B5;8, A>45@60I85 :0;LF89, B0:85 :0: @0AB2>@ 8=35@0 8;8
@0AB2>@ 0@B<0=0, 4;O @0AB2>@5=8O F5DB@80:A>=0 2> D;0:>=0E 8;8 4;O @072545=8O
2>AAB0=>2;5==>3> @0AB2>@0 4;O 2=CB@825==>3> 22545=8O 2 A2O78 A 25@>OB=>ABLN
>1@07>20=8O ?@5F8?8B0B>2 :0;LF852KE A>;59 F5DB@80:A>=0. >7=8:=>25=85 ?@5F8?8B0B>2
:0;LF852KE A>;59 F5DB@80:A>=0 B0:65 <>65B ?@>8AE>48BL ?@8 A<5H820=88 F5DB@80:A>=0 A
@0AB2>@0<8, A>45@60I8<8 :0;LF89 2 >4=>9 8=DC78>==>9 A8AB5<5 4;O 2=CB@825==>3> 22545=8O.
@5?0@0B =5;L7O >4=>2@5<5==> 22>48BL A @0AB2>@0<8, A>45@60I8<8 :0;LF89, 2 B<< G8A;5 A
4;8B5;L=K<8 8=DC78O<8, A>45@60I85 :0;LF89, =0?@8<5@, ?0@5=B5@0;L=>5 ?8B0=85. 4=0:>, 70
8A.;NG5=85< =>2>@>645==KE, F5DB@80:A>= 8 :0;LF89A>45@60I85 @0AB2>@K <>6=> 22>48BL
?>A;54>20B5;L=>, 5A;8 8=DC78>==CN A8AB5 ?@>

>I>G=K5 @50:F88.

=D5:F88: <8:>7 ?>;>2KE ?CB59, 2>7<>6=0 AC?5@8=D5:F8O @07;8G=>9 ;>:0;870F88, 2K720==0O
4@>660<8, 3@81:0<8 8;8 4@C38<8 @578AB5=B=K<8 <8:@>>@30=87<0<8.
!> AB>@>=K A8AB528 8 ;89 A8AB5 =59B@>?5=8O, ;59:>?5=8O, 3@0=C;>F8B>?5=8O, M>78=>D8;8O,
B@><1>F8B>?5=8O, 0=5<8O (2.;NG0O 35<>;8B8G5A:CN 0=5<8N), ?@>;>=30F8O ?@>B@><18=>2>3>
2@5<5=8, =0@CH5=85 :>03C;OF88, 03@0=C;>F8B>7. > 2@53> ;5G5=8O A;54C5B @53C;O@=>
:=B@>;8@>20BL :0@B8=C :@>28.

!> AB>@>=K 8<9 A8AB5 0=0D8;0:B8G5A:89 H>., 0=0D8;0:B8G5A:85 @50:F88, 0=0D8;0:B>84=K5
@50:F88, 38?5@GC2AB28B5;L=>ABL.

!> AB>@>=K =5@2=>9 A8AB5 3>;>2=0O 1>;L, 3>;>2>:@C65=85, AC4>@>38.

!> AB>@>=K >@30=>2 A;CE0 8 @02=>25A8O: 25@B83>.

!> AB>@>=K >@30=>2 4KE0=8O, 3@C4=>9 ;:5B:8 8 A@54>AB5=8O: 1@>=E>A?07

!> AB>@>=K ?8I520@8B5;L=>3> B@0:B0: AB<0B8B, 3;>AA8B, =5>D>@<;5==K9 :0; 8;8 480@5O,
B>H=>B0, @2>B0, ?0=:@50B8B (2>7<>6=>, 2K720==K9 >1AB@C:F859 65;G=KE ?@>B>:>2). "0:85
?>1>G=K5 @50:F88, :0: ?@028;>, ;53:85 8 G0AB> 8AG570NB 2 B5G5=85 8;8 ?>A;5 ?@5:@0I5=8O
;5G5=8O. A524<5<1@0=>7=K9 :>;8B, 2 >A=>2=>< 2K720=K9 Clostridium difficile >;LH8=AB2> 87 MB8E
1>;L=KE 8<5;8 D0:B>@K @8A:0 70AB>O 2 65;G52K2>4OI8E ?CBOE, =0?@8<5@, ;5G5=85 2 0=0<=575,
BO65;K5 701>;520=8O 8 ?>;=>ABLN ?0@5=B5@0;L=>5 ?8B0=85.

@8 MB><=5;L7O 8A.;NG0BL @>;L ?@5F8?8B0B>2, >1@07>202H85AO ?>4 459AB285< F5DB@80:A>=0
2 65;G52K2>4OI8E ?CBOE, 2 @0728B88 ?0=:@50B8B0.

!> AB>@>=K 35?0B>18;80@=>9 A8AB5 C25;8G5=85 :>;8G5AB20 D5@<5=B>2 ?5G5=8 2 AK2>@>B:5
:@>28 (!", ", I5;>G=0O D>AD0B070), O45@=0O 65;BCE0. 01;N40;0AL ?@5F8?8B0F8O F5DB@80:A>=0
:0;LF852>9 A>;8 2 65;G=>< ?C7K@5, G0I5 2A53> C ?0F85=B>2, ?>;CG02H8E ;5G5=85 4>70<8,
?@52KH0NI8<8 @5:><5=4>20==CN AB0=40@B=CN 4>7C. # 45B59 2 ?@>A?5:B82=KE 8AA;54>20=8OE
?@8 2=CB@825==>< ?@8<5=5=88 ?@5?0@0B0 =01;N40;0AL @07=0O G0AB>B0 >1@07>20=8O
?@5F8?8B0B0, 2 =5:>B>@KE 8AA;54>20=8OE 1>;55 30 %. '0AB>B0 >1@07>20=8O ?@5F8?8B0B0
<5=LH5 ?@8 ?@>2545=88 <54;5==>9 8=DC788 (20-30 <8=CB). -B>B MDD5:B, :0: ?@028;>, 0A8
<0B8G5A:89, => 2 @54:8E A;CG0OE ?@5F8?8B0F8O A>?@>2>6405BAO B0:8<8 ;:8=8G5A:8<8 A8<0<8 :0:
1>;L, B>H=>B0 8 @2>B0. MB8E A;CG0OE @5:><5=4>20=> A8<0B8G5A:>5 ;5G5=85. @5F8?8B0F8O, :0:
?@028;>, O2;O5BAO >1@0B8<>9 ?>A;5 >B<5=K F5DB@80:A>=0.

!> AB>@>=K :>68 8 ?>4:>6=>9 :;5BG0B:8: 0;;5@38G5A:85 :>6=K5 @50:F88, B0:85 :0: 2KAK?0=8O, 2 B.G. <0:C;>?0?C;57=K5, :@0?82=8F0, 0;;5@38G5A:89 45@<0B8B, 7C4, >B5:. C;LB8D>@<=0O M@8B5<0, A8=4@>< !B825=A0-6>=A>=0, A8=4@>< 095;;0/B>:A8G5A:89 M?845@<0;L=K9 =5:@>;87, >AB@K9 35=5@0;87>20==K9 M:75<0B>7=K9 ?CABC;57.

!> AB>@>=K <>G52K45;8B5;L=>9 A8AB5 >;83C@8O, 3;N:>7C@8O, 35<0BC@8O. @5F8?8B0B 2 ?>G:0E, ?@58 C 45B59 2 2>7@0AB5 >B 3 ;5B, :>B>@KE ;5G8;8 2KA>:8<8 ACB>G=K<8 4>70<8 (80 <3/:3/ACB 8 1>;55) 8;8 >1I8<8 4>70<8, ?@52KH0N18<8 10 3, 0 B0:65 A 4@C38<8 D0:B>@0<8 @8A:0, B0:8<8 :0: 45384@0B0F8O 8;8 8<<18;870F8O. 1@07>20=85 ?@5F8?8B0B0 2 ?>G:0E O2;O5BAO >1@0B8 ?@5:@0I5=8O ?@8<5=5=8O F5DB@80:A>=0. A2O78 A MB8< A>>1I0;>AL >1 0=C@88 8 =0@CH5=85 DC=:F88 ?>G5:.

I185 =0@CH5=8O: >7=>1, ?8@5:A8O.

50:F88 2 <5AB5 22545=8O: <>65B @072820BLAO D;518B 8 1>;L 2 <5AB5 8=J5:F88 ?>A;5 2=CB@825==>3> 22545=8O, GB> <>6=> <8=8<878@>20BL <54;5==>9 8=J5:F859 2 B5G5=85 ?> :@09=59 <5@5 2-4 <8=CB. □=CB@8=J5:F8O 157 ?@8<5=5=8O ;84>:08=0 1>;57=5==0.

;8O=85 =0 @57C;LB0BK ;01>@0B>@=KE ?>:070B5;59: ?>2KH5=85 C@>2=O :@50B8=8=0 2 :@>28, ;>6=>?>;>68B5;L=K9 B5AB C<1A0. 0: 8 4@C385 0=B818>B8:8, F5DB@80:A>= <>65B 2K7K20BL ;>6=>?>;>68B5;L=K9 @57C;LB0B ?@>1K =0 30;0:B>75<8N. >6=>?>;>68B5;L=K5 @57C;LB0BK <>3CB 1KBL ?>;CG5=K 8 ?@8 >?@545;5=88 3;N:>7K 2 <>G5, ?>MB> 2@5&5DB@80:A>=>3;N:>7C@8N, 2 A;CG05 =5>1E>48<>AB8, A;54C5B >?@545;OBL B>;L:> D5@<5=B=K< <5B>4> 708<>459AB285 A :0;LF85

54:85 A;CG08 BO65;KE =565;0B5;L=KE @50:F89, 8=>340 A ;5B0;L=K< 8AE>4><, 70@538AB@8@>20==K5 C =54>=>H5==KE 8 4>=>H5==KE =>2>@>645==KE (2 2>7@0AB5 < 28 4=59), :>B>@K< 2=CB@825==> 22>48;8 F5DB@80:A>= 8 ?@5?0@0BK :0;LF8O. @8 0CB>?A88 2 ;53:8E 8 ?>G:0E 1K;8 >1=0@C65=K ?@5F8?8B0BK :0;LF852>9 A>;8 F5DB@80:A>=0. KA>:89 @8A: >1@07>20=8O ?@5F8?8B0B>2 C =>2>@>645==KE O2;O5BAO A;54AB285< 8E <0;>3> >1J5<0 :@>28 8 1>;55 ?@>4>;68B5;L=>3>, G5< C 27@>A;KE, ?5@8>40 ?>;C2K2545=8O F5DB@80:A>=0 (A B82>?>:070=8O), «A>15==>AB8 ?@8<5=5=8O»).

0@538AB@8@>20=K A;CG08 >1@07>20=8O ?@5F8?8B0B>2 2 ?>G:0E, ?@58 C 45B59 2 2>7@0AB5 >B 3 ;5B, ?>;CG02H8E 1>;LH85 ACB>G=K5 4>7K ?@5?0@0B0 (=0?@8<5@ ≥ 80 <3/:3/ACB) 8;8 >1I85 4>7K 1>;55 10 3@0<<2, 0 B0:65 8<52H8E 4>?>;=8B5;L=K5 D0:B>@K @8A:0 (=0?@8<5@, >3@0=8G5==>5 ?>B@51;5=85 684:>AB8 8;8 ?>AB5;L=K9 @568<). 8A: >1@07>20=8O ?@5F8?8B0B>2 2>7@0AB05B C ?0F85=B>2, ;8H5==KE ?>4286=>AB8 8;8 C 1>;L=KE 2 A>AB>O=88 >1572>6820=8O. @5F8?8B0BK <>3CB A>?@>2>640BLAO A8<0<8 8;8 1KBL 15AA8<=K<8, <>3CB ?@82>48BL : ?>G5G=>9 =54>AB0B>G=>AB8 8 0=C@88, 8 8AG570NB ?>A;5 ?@5:@0I5=8O ?@8<5=5=8O F5DB@80:A>=0 (A 15==>AB8 ?@8<5=5=8O»).

0@538AB@8@>20=K A;CG08 >1@07>20=8O ?@5F8?8B0B>2 :0;LF852>9 A>;8 F5DB@80:A>=0 2 65;G=> < ?C7K@5, ?@58 C ?0F85=B>2, :>B>@K< ?@5?0@0B 22>48;8 2 4>70E, ?@52KH0N18E AB0=40@B=CN @5:><5=4>20==CN 4>7C. # 45B59, ?> 40==K< ?@>A?5:B82=KE 8AA;54>20=89, G0AB>B0 >1@07>20=8O ?@5F8?8B0B>2 ?@8 2=CB@825==>< 22545=88 ?@5?0@0B0 1K;0 @07=>9 2 =5:>B>@KE 8AA;54>20=8OE 1>;55 30 %. @8 <54;5==>< 22545=88 ?@5?0@0B0 (2 B5G5=85 20-30 <8=CB) G0AB>B0 >1@07>20=8O ?@5F8?8B0B>2, >G5284=>, =865. 1@07>20=85 ?@5F8?8B0B>2 >1KG=> =5 A>?@>2>6405BAO A8<0<8, => 2 @54:8E A;CG0OE 2>7=8:0;8 B0:85 ;;8=8G5A:85 A8;L, B>H=>B0 8 @2>B0. B0:8E A;CG0OE @5:><5=4C5BAO A8<0B8G5A:>5 ;5G5=85. >A;5 ?@5:@0I5=8O ?@8<5=5=8O F5DB@80:A>=0 ?@5F8?8B0BK >1KG=> 8AG570NB (A15==>AB8 ?@8<5=5=8O»).

5@54>78@>2:0.

!8 2>7<>6=K ;8E>@04:0, ;59:>?5=8O, B@><1>F8B>?5=8O, >AB@0O 35<>;8B8G5A:0O 0=5<8O, :>6=K5, 65;C4>G=>.:8H5G=K5 @50:F88 8 @50:F88 ?5G5=8, >4KH:0, ?>G5G=0O =54>AB0B>G=>ABL, AB> <0B8B, 0=>@5:A8O, 2@5<5==0O ?>B5@O A;CE0, ?>B5@O >@85=B0F88 2 ?@>AB@0=AB25. 5G5=85: ?@>2>4OB A8<0B8G5A:CN 8 ?>445@6820NICN B5@0?8N. !?5F8D8G5A:>3> 0=B84>B0 =5B. 5 <>480;87 8 ?5@8B>=50;L=K9 480;87 =5MDD5:B82=K.

@8<5=5=85 2 ?5@8>4 15@5<5==>AB8 8;8 :>@<;5=8O 3@C4LN.

5@5<5==>ABL.

&5DB@80:A>=?@>=8:05B G5@57 ?;0F5=B0@=K9 10@L5@. !CI5AB2CNB >3@0=8G5==K5 40==K5 ?>
?@8<5=5=8N F5DB@80:A>=0 15@5<5==K< 65=I8=020=8O =0 682>B=KE =5 A2845B5;LAB2CNB >
=5?>A@54AB25==>< 8;8 :>A25==>< 2@54=>< 2>7459AB288 =0 M<1@8>=?/?;>4, ?5@8- 8
?>AB=0B0;L=>5 @0728B85. > 2@5
>@<;5=85 3@C4LN.

&5DB@80:A>=?@>=8:05B 2 3@C4=>5 <>;> 2 =87:8E :>=F5=B@0F8OE, => ?@8 ?@8<5=5=88
?@5?0@0B0 2 B5@0?52B8G5A:8E 4>70E =5 >68405BAO =8:0>3> 2;8O=8O =0 3@C4=KE <;045=F52.
4=0:> =5;L7O 8A.;NG0BL @8A: @0728B8O 480@58 8 3@81:>2>9 8=D5:F88 A;878ABKE >1>;>G5:.
!;54C5B CG8BK20BL 2>7<>6=>ABL A5=A818;870F88. C6=> ?@8=OBL @5H5=85 > ?@5:@0I5=88 :>@
<;5=8O 3@C4LN 8;8 >B:070 >B ?@8<5=5=8O F5DB@80:A>=0 A CG5B< ?>;L7K >B 3@C4=>3> 2A:0@
<;820=8O 4;O @515=:0 8 ?>;L7K >B B5@0?88 4;O 65=I8=K.

\$5@B8;L=>ABL.

8AA;54>20=8OE @5?@>4C:B82=>9 DC=:F88 =5 1K;> 2KO2;5=> ?@87=0:>2 =565;0B5;L=>3> 2;8O=8O =0
ABL.

5B8.

@5?0@0B ?@8<5=ONB 45BO< A>3;0A=> 4>78@>2>;, C:070==KE 2 @0745;5 <!>A>1 ?@8<5=5=8O 8
4>7K».

A>15==>AB8 ?@8<5=5=8O.

50:F88 38?5@GC2AB28B5;L=>AB8.

0: 8 ?@8 ?@8<5=5=88 2A5E 15B0-;0:B0<=KE 0=B818>B8;>2, A>>1I0;>AL > A;CG0OE A5@L57=KE
@50:F89 38?5@GC2AB28B5;L=>AB8, 8=>340 A ;5B0;L=K< 8AE>4<< (A1>G=K5 @50:F88»). A;CG05
BO65;KE @50:F89 38?5@GC2AB28B5;L=>AB8 ?@8<5=5=85 F5DB@80:A>=0 A;54C5B =5<54;5==>
?@5:@0B8BL 8 ?@8=OBL A>>B25BAB2CNI85 =5>B;>6=K5 <5@K. 5@54 =0G0;<< ;5G5=8O A;54C5B
CAB0=>28BL, 5ABL ;8 C ?0F85=B0 2 0=0<=575 BO65;K5 @50:F88 38?5@GC2AB28B5;L=>AB8 :
F5DB@80:A>=C, 4@C38< F5D0;>A?>@8=0< 8;8 4@C38< B8?0< 15B0-;0:B0<=KE A@54AB2. !;54C5B A
>AB>@>6=>ABLN ?@8<5=OBL F5DB@80:A>=?0F85=B0< A =0;8G85< 2 0=0<=575 =5BO65;>9
38?5@GC2AB28B5;L=>AB8 : 4@C38< 15B0-;0:B0<=K< ?@5?0@0B0
0@538AB@8@>20=K A;CG08 BO65;KE ?>1>G=KE @50:F89 A> AB>@>=K :>68 (A8=4@<< !B825=A0-
6=>A>=0 8;8 A8=4@<< 095;;0/B>:A8G5A:89 M?845@<0;L=K9 =5:@>;87); >4=0:> G0AB>B0 MB8E
O2;5=89 =58725AB=0 (A1>G=K5 @50:F88»).

708<>459AB285 A ;5:0@AB25==K<8 A@54AB20<8, A>45@60I8<8 :0;LF89.

=54>=>H5==KE 8 4>=>H5==KE <;045=F52 2 2>7@0AB5 4> 1 <5AOF0 >?8A0=K A;CG08 >1@07>20=8O
?@5F8?8B0B>2 :0;LF852>9 A>;8 F5DB@80:A>=0 2 ;53:8E 8 ?>G:0E A ;5B0;L=K< 8AE>4> <5=LH59 <5@5
>4=>2 F5DB@80:A>= 8 :0;LF89 22>48;8 2 @07=>5 2@5 @07=K< 2=CB@825==K< 8=DC78>==K< A8AB5
<03;0A=> 8<5NI8in vitro 1K;> ?>:070=>, GB=>=>2>@>645==K< 3@>78B ?>2KH5==K9 @8A:
>1@07>20=8O ?@5F8?8B0B>2 :0;LF852>9 A>;8 F5DB@80:A>=0 ?> A@02=5=8N A ?0F85=B0<8 4@C38E
2>7@0AB=KE 3@C??.

@8 ?@8<5=5=88 F5DB@80:A>=0 ?0F85=B0< ;N1>3> 2>7@0AB0 ?@5?0@0B =5;L7O A<5H820BL 8;8
22>48BL >4=>2@5<5==> A ;N1K<8 @0AB2>@0<8 4;O 2=CB@825==>3> 22545=8O, A>45@60I8<8
<0;LF89, 4065 ?@8 8A?>;L7>20=88 @07;8G=KE 8=DC78>==KE A8AB5< 8;8 22545=88 ?@5?0@0B>2 2
@07;8G=K5 8=DC78>==K5 CG0AB:8. 4=0:> ?0F85=B0< 2 2>7@0AB5 AB0@H5 28 4=59 F5DB@80:A>= 8
<0;LF89A>45@60I85 @0AB2>@K <>6=> 22>48BL ?>A;54>20B5;L=>, 4@C3 ?>A;5 4@C30, ?@8 CA;>288
22545=8O ?@5?0@0B>2 G5@57 @07;8G=K5 8=DC78>==K5 A8AB5==>9 A8AB5AB>O==KE 8=DC78OE
<0;LF89A>45@60I8E @0AB2>@>2 4;O ?>;=>3> ?0@5=B5@0;L=>3> ?8B0=8O (%), <548F8=A:85
@01>B=8:8 <>3CB =07=0G8BL 0;LB5@=0B82=K5 0=B810:B5@80;L=K5 A@54AB20, ?@8<5=5=85
>B>@KE =5 A2O70=> A ?>4>1=K< @8A:<< >1@07>20=8O ?@5F8?8B0B>2. A;8 ?@8<5=5=85
F5DB@80:A>=0 ?0F85=B0<, :>B>@K5 =C640NBAO 2 ?>AB>O==>< ?8B0=88, ?@87=0=> =5>1E>48=0 8
?@>==K5 A8AB5B82>?>:070=8O», <<>1>G=K5 @50:F88» 8 «5A>2<5AB8<>ABL»).

5B8.

57>?0A=>ABL 8 MDD5:B82=>ABL F5DB@80:A>=0 C =>2>@>645==KE, <;045=F52 8 45B59 1K;8 CAB0=>2;5=K 4;O 4>7, >?8A0==KE 2 @0745;5 «!>A>1 ?@<5=5=8O 8 4>7K». 8AA;54>20=8OE 1K;> ?>:070=>, GB> F5DB@80:A>=, :0: =5:>B>@K5 4@C385 F5D0;>A?>@8=K, <>65B 2KB5A=OBL 18;8@C18= 87 A2O78 A 0;L1C<8=>< AK2>@>B:8 :@>28.
@5?0@0B ?@>B82>?>:070= =54=>H5==K< 8 4>=>H5==K< =>2>@>645==K<, :>B>@K< 3@>78B @8A: @0728B8O 18;8@C18=>2>9 M=F5D0;>?0B88 (AB82>?>:070=8O»).
<>?>A@54>20==0O 35<>;8B8G5A:0O 0=5<8O.
!;CG08 8<>?>A@54>20==>9 35<>;8B8G5A:>9 0=5<88 =01;N40;8AL C ?0F85=B>2, ?>;CG02H8E 0=B810:B5@80;L=K5 A@54AB20 ;:0AA0 F5D0;>A?>@8=>2 (A1>G=K5 @50:F88»). "O65;K5 A;CG08 35 <>;8B8G5A:>9 0=5<88, 2 B>< G8A;5 A ;5B0;L=K< 8AE>4><, 1K;8 70@538AB@8@>20=K 2 ?5@8>4 ;5G5=8O F5DB@80:A>=>< :0: C 27@>A;KE, B0: 8 C 45B59.
A;8 2> 2@5
;8B5;L=>5 ;5G5=85.
@8 4;8B5;L=>< ;5G5=88 A;54C5B @53C;O@=> ?@>2>48BL @0725@=CBK9 0=0;87 :@>28.
&5DB@80:A>= <>65B C25;8G820BL ?@>B@><18=>2>5 2@5
>;8B/G@57<5@=K9 @>AB =5GC2AB28B5;L=KE <8:@>>@30=87<>2.
!;CG08 :>;8B0 8 ?A524><5<1@0=>7=>3> :>;8B0, 0AA>F88@>20==KE A ?@<5=5=85< 0=B810:B5@80;L=KE A@54AB2, 1K;8 70@538AB@8@>20=K =0 D>=5 ?@<5=5=8O ?>GB8 2A5E 0=B810:B5@80;L=KE A@54AB2, 2 B>< G8A;5 F5DB@80:A>=0. "O65ABL MB8E 701>;520=89 <>65B :>;510BLAO >B ;53:>9 4> C3@>60NI59 687=8. >MB> CG8BK20BL 2>7<>6=>ABL B0:>3> 4803=>70 C ?0F85=B>2, C :>B>@KE 2> 2@5A;5 ?@<5=5=8O F5DB@80:A>=0 2>7=8:;0 480@5O (A1>G=K5 @50:F88»). !;54C5B >14C<0BL ?@5:@0I5=85 B5@0?88 F5DB@80A:>=>< 8 ?@<5=5=85 A>>B25BAB2CNI8E A@54AB2 ?@>B82 Clostridium difficile 5:0@AB25==K5 A@54AB20, ?>402;ONI85 ?5@8AB0;LB8:C, ?@<5=OBL =5 A;54C5B.
0: 8 ?@8 ?@<5=5=88 4@C38E 0=B810:B5@80;L=KE A@54AB2, <>3CB 2>7=8:0BL AC?5@8=D5:F88, 2K720==K5 =5GC2AB28B5;L=K<8 : ?@5?0@0BC <8:@>>@30=87<0<8 (M=B5@>: :8 8 HB0<Candida). &5DB@80:A>= =C6=> A >AB>@>6=>ABLN ?@<5=OBL ?0F85=B0< A 65;C4>G=>:8H5G=K<8 701>;520=8O<8 2 0=0<=575, 2 G0AB=>AB8 :>;8B>
"O65;0O ?>G5G=0O 8 ?5G5=>G=0O =54>AB0B>G=>ABL.
A;CG05 BO65;>9 ?>G5G=>9 8 ?5G5=>G=>9 =54>AB0B>G=>AB8 @5:><5=4C5BAO BI0B5;L=K9 ;:8=8G5A:89 <>=8B>@8=3 157>?0A=>AB8 8 MDD5:B82=>AB8 ?@5?0@0B0 (AA>1 ?@<5=5=8O 8 4>7K»). !;54C5B A>1;N40BL >AB>@>6=>ABL ?@8 ?@<5=5=88 F5DB@80:A>=0 1>;L=K< A ?>G5G=>9 =54>AB0B>G=>ABLN, :>B>@K5 >4=>2@5<5==> ?>;CG0NB 0<8=>3;8:>784K 8 48C@5B8:8.
;8O=85 =0 @57C;LB0BK A5@>;>38G5A:8E 8AA;54>20=89.
@8 ?@<5=5=88 F5DB@80:A>=0 B5AB C<1A0 <>65B 4020BL ;>6=>?>;>68B5;L=K5 @57C;LB0BK. "0:65 ?@5?0@0B <>65B 2K7K20BL ;>6=>?>;>68B5;L=K5 @57C;LB0BK 0=0;870 =0 =0;8G85 30;0:B>75<88 (A 1>G=K5 @50:F88»).
@8 >?@545;5=88 3;N:>7K 2 <>G5 =5D5@<5=B=K<8 <5B>40<8 <>3CB 1KBL ?>;CG5=K ;>6=>?>;>68B5;L=K5 @57C;LB0BK. B5G5=85 ?@<5=5=8O F5DB@80:A>=0 C@>2=8 3;N:>7K 2 <>G5 A;54C5B ?>@545;OBL A ?>>ILN D5@<5=B=KE <5B>4>2 0=0;870 (A1>G=K5 @50:F88»).
0B@89.
064K9 3@0<< ?@5?0@0B0 A>45@68B 3,6 <<>;L =0B@8O. -B> A;54C5B CG8BK20BL ?0F85=B0<, :>B>@K5 ?@845@6820NBAO 485BK A :>=B@>;8@C5
!/?5:B@ 0=B810:B5@80;L=>9 0:B82=>AB8.
&5DB@80:A>= 8<55B >3@0=8G5==K9 A?5:B@ 0=B810:B5@80;L=>9 0:B82=>AB8 8 <>65B 1KBL =5?@83>4=K< 4;O ?@<5=5=8O 2 :0G5AB25 <>=>B5@0?88 ?@8 ;5G5=88 ?>@545;5==KE B8?>2 8=D5:F88, :@><5 A;CG052, :>340 2>71C48B5;L C65 ?>4B25@645= (AA>1 ?@<5=5=8O 8 4>7K»). A;CG05 ?>;8<8:@>1=KE 8=D5:F89, :>340 A@548 ?>4>7@520571C48B5;59 5ABL @578AB5B=K5 : F5DB@80:A>=C <8:@>>@30=87
@<5=5=85 ;84>:08=0.
A;8 2 :0G5AB25 @0AB2>@8B5;O ?@<5=ONB @0AB2>@ ;84>:08=0, F5DB@80:A>= <>6=> 22>48BL B>;L:> 2=CB@8. 5@54 22545=85< ?@5?0@0B0 A;54C5B >1O70B5;L=> CG5ABL ?@>B82>?>:070=8O : ?@<5=5=8N ;84>:08=0, ?@54>AB5@565=8O 8 4@C3CN A>>B25BAB2CNICN 8=D>@<0F8N, ?@82545==CN 2 8=AB@C:F88 4;O <548F8=A:>3> ?@<5=5=8O ;84>:08=0 (AB82>?>:070=8O»). @8 2=CB@8A;5 C:>;0 @5:><5=4C5BAO 872;5GL ?>@H5=L H?@8F0 (=5 4>;6=0 ?>O2;OBLAO :@>2L),

GB>1K C1548BLAO, GB> 83;0 =5 ?>?0;0 2 :@>25=>A=K9 A>AC4. !;54C5B 8A?>;L7>20BL
A2565?@83>B>2;5==K5 @0AB2>@K. 0AB2>@ ;84>:08=0 =8 2 :>5< A;CG05 =5;L7O 22>48BL
2=CB@825==>.

5;G=>:0<5==0O 1>;57=L.

A;CG05 =0;8G8O =0 A>=>3@0<<5 B5=59, A;54C5B CG5ABL 2>7<>6=>ABL >1@07>20=8O
?@5F8?8B0B>2 :0;LF852>9 A>;8 F5DB@80:A>=0. 0B5=5=8O, :>B>@K5 >H81>G=> AG8B0;8AL 65;G=K
<8 :0<=O<8, =01;N40;8AL =0 A>=>3@0<<5 65;G=>3> ?C7K@O, 8 G0AB>B0 8E 2>7=8:=>25=8O
2>7@0AB0;0 ?@8 ?@8<5=5=88 F5DB@80:A>=0 2 4>75 1 3/ACB 8 2KH5. A>1CN >AB>@>6=>ABL
A;54C5B A>1;N40BL ?@8 ?@8<5=5=88 ?@5?0@0B0 C 45B59. 5BO< =5 A;54C5B ?@8<5=OBL 4>7K 2KH5
80 <3/:3 <0AAK B5;0, B0: :0 ?>2KH05BAO @8A: >1@07>20=8O 65;G=>3> ?@5F8?8B0B0. "0:85
?@5F8?8B0BK 8AG570NB ?>A;5 ?@5:@0I5=8O B5@0?88 F5DB@80:A>=>1@07>20=85 ?@5F8?8B0B>2
:0;LF852>9 A>;8 F5DB@80:A>=0 A>?@>2>640;>AL A8<0B8:>9. @8 =0;8G88 A8<>2 @5:><5=4C5BAO
:=>A5@20B82=>5 =5E8@C@38G5A:>5 ;5G5=85, 8 2@0G 4>;65= ?@8=OBL @5H5=85 > ?@5:@0I5=88
?@8<5=5=8O ?@5?0@0B0, >?8@0OAL =0 @57C;LB0BK >F5=:8 ?>;L7K-@8A:0 :=:@5B=>3> A;CG0O (A
1>G=K5 @50:F88»).

5;G=K9 AB07.

!;CG08 ?0=@50B8B0, 2>7<>6=> 2K720==K5 =5?@>E>48<>ABLN 65;G=KE ?CB59, 1K;8
70@538AB@8@>20=K C ?0F85=B>2, ?>;CG02H8E F5DB@80:A>= (A1>G=K5 @50:F88»). >;LH8=AB2>
87 B0:8E ?0F85=B>2 8<5;8 D0:B>@K @8A:0 @0728B8O E>;5AB070 8 >1@07>20=8O 18;80@=>3>
A;0460, B0:85 :0: ?@54K4CI0O 7=0G8B5;L=0O B5@0?8O, BO65;0O 1>;57=L 8 ?>;=>5 ?0@5=B5@0;L=>5
?8B0=85. 5;L7O 8A.;NG0BL, GB> 8=8F88@CNI8< 8;8 4>?>;=8B5;L=K< D0:B>@< @0728B8O MB>3>
=0@CH5=8O <>65B 1KBL >1@07>20=85 2 65;G=KE ?CBOE ?@5F8?8B0B>2 2 @57C;LB0B5 ?@8
<5=5=8O F5DB@80:A>=0.

>G5G=>:0<5==0O 1>;57=L.

0@538AB@8@>20=K A;CG08 >1@07>20=8O ?>G5G=KE :0<=59, :>B>@K5 8AG570;8 ?>A;5 >B<5=K
F5DB@80:A>=0 (A1>G=K5 @50:F88»). A;CG05 =0;8G8O A8<>2 A;54C5B A45;0BL C;LB@072C:>2>5
>1A;54>20=85. 5H5=85 > ?@8<5=5=88 ?@5?0@0B0 ?0F85=B0< A =0;8G85< 2 0=0<=575 ?>G5G=KE :0
<=59 8;8 38?5@:0;LF8C@88 ?@8=8<05B 2@0G, >?8@0OAL =0 @57C;LB0BK >F5=:8 ?>;L7K-@8A:0 2
:064>< :=:@5B=>< A;CG05.

**!>A>1=>ABL 2;8OBL =0 A:>@>ABL @50:F88 ?@8 C?@02;5=88 02B>B@0=A?>@B< 8;8 @01>B5 A
4@C38<8 <5E0=87<0<8.**

!>>B25BAB2CNI85 8AA;54>20=8O =5 ?@>2>48;8AL. A2O78 A 2>7<>6=>ABLN 2>7=8:=>25=8O B0:8E
?>1>G=KE @50:F89, :0: 3>;>2>:@C65=85, F5DB@80:A>= <>65B 2;8OBL =0 A?>A>1=>ABL C?@02;OBL
B@0=A?>@B=K<8 A@54AB20<8 8;8 @01>B0BL A <5E0=87<0<8.

708<>459AB285 A 4@C38<8 ;5:0@AB25==K<8 A@54AB20<8 8 4@C385 284K 2708<>459AB289.

0AB2>@8B5;8, A>45@60I85 :0;LF89, B0:85 :0: @0AB2>@ 8=35@0 8;8 @0AB2>@ 0@B<0=0, =5 A;54C5B
8A?>;L7>20BL 4;O 2>AAB0=>2;5=8O ?@5?0@0B0 2> D;0:>=0E 8;8 4;O 40;L=59H53> @072545=8O
2>AAB0=>2;5==>3> @0AB2>@0 4;O 2=CB@825==>3> 22545=8O, ?>A:>;L:C <>65B >1@07>20BLAO
?@5F8?8B0B. @5F8?8B0BK :0;LF852>9 A>;8 F5DB@80:A>=0 B0:65 <>3CB >1@07>2K20BLAO ?@8 A
<5H820=88 F5DB@80:A>=0 A :0;LF89A>45@60I8<8 @0AB2>@0<8 2 >4=>9 8=DC78>==>9 A8AB5<5.
&5DB@80:A>= =5;L7O 22>48BL >4=>2@5<5==> A @0AB2>@0<8 4;O 2=CB@825==>3> 22545=8O,
A>45@60I8<8 :0;LF89, 2 B>< G8A;5 A :0;LF89A>45@60I8<8 @0AB2>@0<8 4;O 4;8B5;L=KE 8=DC789,
B0:8<8 :0: @0AB2>@K 4;O ?0@5=B5@0;L=>3> ?8B0=8O, A ?><>ILN Y->1@07=>9 A8AB5>AB0;L=K<
?0F85=B0<, :@><5 =>2>@>645==KE, F5DB@80:A>= 8 :0;LF89A>45@60I85 @0AB2>@K <>6=> 22>48BL
?>A;54>20B5;L=>, >48= 70 4@C38<, 5A;8 <564C 8=DC78O<8 BI0B5;L=> ?@>2<5AB8<>9 684:>ABLN.
8AA;54>20=8OE in vitro A 8A?>;L7>20=85< ?;0728==>9 :@>28 27@>A;KE 8 =>2>@>645==KE 1K;>
?>:070=>, GB> =>2>@>645==K< 3@>78B ?>2KH5==K9 @8A: >1@07>20=8O ?@5F8?8B0B>2 :0;LF852>9
A>;8 F5DB@80:A>=0 (AA>1 ?@8<5=5=8O 8 4>7K), «@>B82?>:070=8O», «A>15==>AB8 ?@8
<5=5=8O», «>1>G=K5 @50:F88»).

<8=>3;8:>784K. !CI5AB2CNB ?@>B82>@5G82K5 40==K5 >B=>A8B5;L=> ?>B5=F80;L=>3> CA8;5=8O
B>:A8G5A:>3> 2>7459AB28O 0<8=>3;8:>784>2 =0 ?>G:8 ?@8 8E ?@8<5=5=88 A F5D0;>A?>@8=0<8.
B0:8E A;CG0OE A;54C5B BI0B5;L=> A>1;N40BL @5:><5=40F88 ?> <>=8B>@8=3C C@>2=O 0
<8=>3;8:>784>2 (8 DC=:F88 ?>G5:) 2 :;8=8G5A:>9 ?@0:B8:5.

5AB5@>84=K5 ?@>B82>2>A?0;8B5;L=K5 A@54AB20, 0=B803@530=BK, 0=B03>=8ABK 28B0<8=0 (=0?@8<5@, 20@D0@8=): ?>2KH5=85 2>7<6=>AB8 :@>2>B5G5=80.
!>2<5AB=>5 ?@8<5=5=85 ?@5?0@0B0 A ?5@>@0;L=K<8 0=B8:>03C;O=B0<8 <>65B CA8;820BL
MDD5:B ?@>B82 28B0<8=0 8 @8A: :@>2>B5G5=80. 5:>5=4C5BAO G0AB> ?@>25@OBL
<564C=0@>4=>5 =>@<0;87>20=>5 >B=>H5=85 8 4>;6=K<>1@07>< :>@>5:B8@>20BL 4>7C
0=B828B0<8=0 :0: 2> 2@5A;5 B5@0?88 F5DB@80:A>=>< (A1>G=K5 @50:F88)).
5B;52K5 48C@5B8:8 8 =5D@>B>:A8G5A:85 ?@5?0@0BK ?>2KH05BAO @8A: =5D@>B>:A8G=>AB8.
0:B5@8>AB0B8G5A:85 0=B818>B8:8 (E:>@0;; B5B@0F8:;8=): A=860NB 10:B5@8F84=K9 MDD5:B
F5DB@80:A>=0. 8AA;54>20=88 *in vitro*?@8 ?@8<5=5=88 E:>@0;0 2 A>G5B0=88 A F5DB@80:A>=><
=01;N40;8AL 0=B03>=8AB8G5A:85 MDD5:BK. ;8=8G5A:00 7=0G8<>ABL MB8E 40==KE =58725AB=0.
>@<>=0;L=K5 :>=B@0F5?B82K: A=8605BAO MDD5:B82=>ABL 3>@<>=0;L=KE :>=B@0F5?B82>2,
?>MB><5=4C5BAO 8A?>;L7>20BL 4>?>;=8B5;L=K5 (=53>@<>=0;L=K5) <5B>4K :>=B@0F5?F88 2> 2@5
@C385 15B0-;0:B0<=K5 0=B818>B8:8: 2>7<6=>AB8 @0728B8O ?5@5:@5AB=KE 0;;5@38G5A:8E
@50:F89.
>A;5 ?@8<5=5=80 MB0=>;0 A@07C ?>A;5 ?@85<0 F5DB@80:A>=0 =5 =01;N40;>AL MDD5:B>2,
?>E>68E =0 459AB285 48AC;LD8@0<0.
&5DB@80:A>= =5 A>45@68B N<5B8;B8>B5B@07>;L=CN 3@C??C, :>B>@0O 1K <>3;0 ?@825AB8 :
=5?5@5=>A8<>AB8 MB0=>;0 8;8 :@>2>B5G5=8N, GB> A2>9AB25=> =5:>B>@K< 4@C38<
F5D0;>A?>@8=0
@>15=5F84: =5 2;8O5B =0 :0=0;LF52CN A5:@5F8N F5DB@80:A>=0 (2 >B;8G85 >B 4@C38E
F5D0;>A?>@8=>2).
0: 8 4@C385 0=B818>B8:8, F5DB@80:A>= <>65B A=860BL B5@0?52B8G5A:89 MDD5:B 20:F8=K
?@>B82 B8D0, >4=0:> B0:>9 MDD5:B @0A?@>AB@0=O5BAO B>;L:> =0 >A;01;5==K9 HB0<< Ty21.
0AB2>@ &5DB@80:A>=-0@=8F0 =5 A;54C5B A<5H820BL 8;8 22>48BL >4=>2@5<5==> A 4@C38<8
0=B8<8:@>1=K<8 ?@5?0@0B0<8 2 A2O78 A D0@<0F52B8G5A:>9 =5A>2<5AB8<>ABLN.
&5DB@80:A>= =5A>2<5AB8< 8 53> =5;L7O A<5H820BL A0<70:@8=><, 20=:><8F8=><, D;C:>=07>;>
< 8 0<8=>3;8:>7840<8.

\$0@<0:>;>38G5A:85 A2>9AB20.

\$0@<0:>48=0<8:0.

&5DB@80:A>= ?0@5=B5@0;L=K9 F5D0;>A?>@8=>2K9 0=B818>B8: III ?>:>;5=8O A ?@>;>=38@>20==K
< 459AB285

8:@>18>;>38O. 0:B5@8F84=0O 0:B82=>ABL F5DB@80:A>=0 >1CA;>2;5=0 ?>402;5=85< A8=B570
::5B>G=KE <5<1@0=. &5DB@80:A>= 0:B825= *in vitro* 2 >B=>H5=88 1>;LH8=AB20 3@0
<>B@8F0B5;L=KE 8 3@0;>68B5;L=KE <8:@>>@30=87<>2. &5DB@80:A>= E0@0:B5@87C5BAO >G5=L
1>;LH>9 CAB>9G82>ABLN : 1>;LH8=AB2C β-;0:B0<07 (:0: ?5=8F8;;8=07, B0: 8 F5D0;>A?>@8=07) 3@0
>68B5;L=KE 8 3@0<>B@8F0B5;L=KE 10:B5@89. &5DB@80:A>= 0:B825= 2 >B=>H5=88 B0:8E
<8:@>>@30=87<>2 *in vitro* 8 ?@8 ;;8=8G5A:8E 8=D5:F8OE (A@0745; <>:070=8O)):

@0;>68B5;L=K5 0M@>1K. *Staphylococcus aureus* (<5B8F8;;8=GC2AB28B5;L=K9), :>03C;07>-
>B@8F0B5;L=K5 AB0D8;>:::8, *Streptococcus pyogenes* (β-35<>;8B8G5A:89, 3@C??K), *Streptococcus*
agalactiae (β-35<>;8B8G5A:89, 3@C??K), β-35<>;8B8G5A:85 AB@5?B>:>::8 (3@C??K =8, =8),
Streptococcus viridans, *Streptococcus pneumoniae*#AB>9G82K5 : <5B8F8;;8=C *Staphylococcus spp.*
@578AB5=B=K5 : F5D0;>A?>@8=0<, 2 B>< 65 G8A;5 : F5DB@80:A>=C. "0:65 *Enterococcus faecalis*,
Enterococcus faecium 8 *Listeria monocytogenes*?@>O2;ONB CAB>9G82>ABL : F5DB@80:A>=C.
@0<>B@8F0B5;L=K5 0M@>1K. *Acinetobacter lwoffii*, *Acinetobacter anitratus* (3;02=K< >1@07><
A. baumannii)*, *Aeromonas hydrophila*, *Alcaligenes faecalis*, *Alcaligenes odorans*, 0;;035=>?>4>1=K5 10:B5@88,
Borrelia burgdorferi, *Capnocytophaga spp*, *Citrobacter diversus* (2;;NG0O *C. amalonaticus*), *Citrobacter freundii**,
Escherichia coli, *Enterobacter aerogenes**, *Enterobacter cloacae**, *Enterobacter spp.* (4@C385)*, *Haemophilus*
ducreyi, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Hafnia alvei*, *Klebsiella oxytoca*, *Klebsiella*
*pneumoniae*** , *Moraxella catarrhalis* (@0=55 =07K20;8AL *Branhamella catarrhalis*), *Moraxella osloensis*,
Moraxella spp. (4@C385), *Morganella morganii*, *Neisseria gonorrhoea*, *Neisseria meningitidis*, *Pasteurella*
multocida, *Plesiomonas shigelloides*, *Proteus mirabilis*, *Proteus penneri**, *Proteus vulgaris**, *Pseudomonas*
*fluorescens**, *Pseudomonas spp.* (4@C385)*, *Providentia rettgeri**, *Providentia spp* (4@C385), *Salmonella typhi*,
Salmonella spp. (=5 B8D>84=K5), *Serratia marcescens**, *Serratia spp.* (4@C385)*, *Shigella spp*, *Vibrio spp*,
Yersinia enterocolitica, *Yersinia spp* (4@C385).

* 5:>B>@K5 87>;OBK MB8E 284>2 CAB>9G82K : F5DB@80:A>=C 3;02=K< >1@07>< 2A;54AB285 >1@07>20=80 β-;0:B0<07, :>48@C5<A><0<8.

** 5:>B>@K5 87>;OBK MB8E 284>2 CAB>9G82K : F5DB@80:A>=C 2A;54AB285 >1@07>20=80 @O40 ?;07<84>->?>A@54>20==KE β-;0:B0<07.

=>385 87 HB0<<>2 2KH5C:070==KE <8:@>>@30=87<>2, 8<5NI8E <=>65AB25==CN CAB>9G82>ABL : B0:8< 0=B818>B8:0< :0: 0<8=>?5=8F8;;8=K 8 C@584>?5=8F8;;8=K, F5D0;>A?>@8=K ?5@2>3> 8 2B>@>3> ?>:>5=80, 0<8=>3;8:>784K, GC2AB28B5;L=K : F5DB@80:A>=C. *Treponema pallidum* GC2AB28B5;L=0 : F5DB@80:A>=C *in vitro* 8 2 >?KB0E =0 682>B=KE. ;8=8G5A:85 8A?KB0=80 ?>:07K20NB, GB> F5DB@80:A>= MDD5:B825= 4;O ;5G5=80 ?5@28G=>3> 8 2B>@8G=>3> A8D8;8A0, 70 8A.;NG5=85< ;8=8G5A:8E HB0<<>2 *P. Aeruginosa*, CAB>9G82KE : F5DB@80:A>=C.

=0M@>1K. *Bacteroides spp.* (GC2AB28B5;L=K5 : 65;G8)*, *Clostridium spp.* (@><5 *C. difficile*), *Fusobacterium nucleatum*, *Fusobacterium spp.* (4@C385), *Gaffkia anaerobica* (@0=55 =07K20;8AL *Peptococcus*), *Peptostreptococcus spp.*

* 5:>B>@K5 87>;OBK MB8E 284>2 CAB>9G82K : F5DB@80:A>=C 2A;54AB285 >1@07>20=80 β-;0:B0 <07.

=>385 87 HB0<<>2 *Bacteroides spp.*, ?@>4CF8@CNI85 β-;0:B0<07K (2 G0AB=>AB8 *B. fragilis*), CAB>9G82K : F5DB@80:A>=C. #AB>9G82K9 *Clostridium difficile*

'C2AB28B5;L=>ABL : F5DB@80:A>=C <>6=> >?@545;OBL <5B>4>< 48A:>2 8;8 <5B>4>< A5@89=KE @072545=89 =0 030@5 8;8 1C;L=>5, 8A?>;L7CO AB0=40@B=CN <5B>48:C, ?>4>1=CN B>9, :>B>@CN @5:><5=4C5B 0F8>=0;L=K9 :><8B5B ;8=8G5A:8E ;01>@0B>@=KE AB0=40@B>2 (!). ;O F5DB@80:A>=0 ! CAB0=>28; A;54CNI85 :@8B5@88 >F5=:8 @57C;LB0B>2 8A?KB0=89:

"01;8F0 1.

	'C2AB28B5;L=K5	#<5@5==> GC2AB28B5;L=K5	!B>9:85
5B>4 @072545=89 =3818@CNI00 :>=F5=B@0F8O, <3/;	≤ 8	16-32	≥ 64
5B>4 48A:>2 (48A: A 30=0) 80<5B@ 7>=K 7045@6:8 @>AB0, <<	≥ 21	20-14	≤ 13

;O >?@545;5=80 GC2AB28B5;L=>AB8 <8:@>>@30=87<>2 =5>1E>48<> 8A?>;L7>20BL 48A:8 A F5DB@80:A>=><, B0: :0: 2 8AA;54>20=8OE *in vitro*?>:070=>, GB> F5DB@80:A>= 0:B825= 2 >B=>H5=88 >B45;L=KE HB0<<>2, :>B>@K5 CAB>9G82K ?@8 8A?>;L7>20=88 48A:>2, ?@54=07=0G5==KE 4;O 2A59 3@C??K F5D0;>A?>@8=>2.

<5AB> AB0=40@B>2 ! 4;O >?@545;5=80 GC2AB28B5;L=>AB8 <8:@>>@30=87<>2 <>6=> 8A?>;L7>20BL 8 4@C385 E>@>H> AB0=40@B87>20==K5 =>@<0B82K, =0?@8<5@ DIN 8 ICS, ?>72>;ONI85 045:20B=> >F5=8BL C@>25=L GC2AB28B5;L=>AB8.

\$0@<0:>:8=5B8:0.

\$0@<0:>:8=5B8:0 F5DB@80:A>=0 8<55B =5;8=59=K9 E0@0:B5@. A5 >A=>2=K5 D0@<0:>:8=5B8G5A:85 ?0@0<5B@K, >A=>20==K5 =0 >1I8E :>=F5=B@0F8OE ?@5?0@0B0, 70 8A.;NG5=85< ?5@8>40 ?>;C2K2545=80, 7028AOB >B 4>7K.

A0AK20=85. 0:A8<0;L=00 :>=F5=B@0F8O 2 ?;07<5 :@>28 ?>A;5 >4=>:@0B=>3> 2=CB@83> 22545=80 1 3 ?@5?0@0B0 A>AB02;O5B 81 <3/; 8 4>AB8305BAO G5@57 2-3 G0A0 ?>A;5 22545=80. 07>2K5 2=CB@825==K5 8=DC788 1 3 8 2 3 ?@5?0@0B0 ?@82>4OBL G5@57 30 <8=CB : :>=F5=B@0F8O< 168,1 ± 28,2 8 256,9 ± 16,8 <3/; A>>B25BAB25==>. ;>I04L ?>4 :@82>9 :>=F5=B@0F88 2 ?;07<5 :@>28 ?>A;5 22545=80 @02=0 B0:>2>9 ?>A;5 2=CB@83> 22545=80. -B> >7=0G05B, GB> 18>4>ABC?=>ABL F5DB@80:A>=0 ?>A;5 2=CB@83> 22545=80 A>AB02;O5B 100 %.

0A?@545;5=85. 1J5< @0A?@545;5=80 F5DB@80:A>=0 A>AB02;O5B 7-12 ;. >A;5 22545=80 2 4>75

1-2 3 F5DB@80:A>= E>@>H> ?@>=8:05B 2 B:0=8 8 684:>AB8 >@30=87<0. 0 ?@>BO65=88 1>;55

24 G0A>2 53> :=F5=B@0F88 =0<=>3> ?@52KH0NB <8=8<0;L=K5 ?>402;ONI85 :=F5=B@0F88 4;O
1>;LH8=AB20 2>71C48B5;59 8=D5:F89 1>;55 G5< 2 60 B:0=OE 8 684:>ABOE (2 B>< G8A;5 ;53:8E,
A5@4F5, 65;G52K2>4OI8E ?CBOE, ?5G5=8, <8=40;8=0E, A@54=5< CE5 8 A;878AB>9 =>A0, :=ABOE, 0
B0:65 A?8==><73>2>9, ?;52@0;L=>9 8 A8=>280;L=>9 684:>ABOE, 2 A5:@5B5 ?@>AB0BK).
>A;5 2=CB@825==>3> 22545=8O F5DB@80:A>= 1KAB@> ?@>=8:05B 2 A?8==><73>2CN 684:>ABL,
345 10:B5@8F84=K5 :=F5=B@0F88 : GC2AB28B5;L=K< <8:@>>@30=87<0< A>E@0=ONBAO 2
B5G5=85

24 G0A>2.

!2O7K20=85 A 15;:0<8. &5DB@80:A>= >1@0B8<> A2O7K205BAO A 0;L1C<8=><, ?@8G5< AB5?5=L
A2O7K20=8O C<5=LH05BAO A @>AB< :=F5=B@0F88, =0?@8<5@, A=860OAL A 95 % ?@8
:=F5=B@0F88 2 ?;07<5 :@>28 <5=55 100 <3/; 4> 85 % ?@8 :=F5=B@0F88 300 <3/; .;03>40@O =87:>9
:=F5=B@0F88 0;L1C<8=0 2 B:0=52>9 684:>AB8 4>;O A2>1>4=>3> F5DB@80:A>=0 2 =59 2KH5, G5< 2
?;07<5 :@>28.

@>=8:=>25=85 2 >B45;L=K5 B:0=8. &5DB@80:A>= ?@>=8:05B G5@57 2>A?0;5==K5 <>73>2K5
>1>;>G:8 C 45B59, 2 B.G. =>2>@>645==KE. '5@57 24 G0A0 ?>A;5 22545=8O F5DB@80:A>=0 2
4>75 50-100 <3/3 <0AAK B5;0 (=2>@>645==K< 8 <;045=F0< A>>B25BAB25==>) :=F5=B@0F88
F5DB@80:A>=0 2 A?8==><73>2>9 684:>AB8 ?@52KH0NB 1,4 <3/;. 0:A8<0;L=0O :=F5=B@0F88 2
A?8==><73>2>9 684:>AB8 4>AB8305BAO ?@8<5@=> G5@57 4 G0A0 ?>A;5 22545=8O 8 A>AB02;O5B 2
A@54=5< 18 <3/;. @8 10:B5@80;L=>< <5=8=38B5 A@54=OO :=F5=B@0F88 F5DB@80:A>=0 2
F5@51@>A?8=0;L=>9 684:>AB8 A>AB02;O5B 17 % >B :=F5=B@0F88 2 ?;07<5 :@>28, ?@8
0A5?B8G5A:>< <5=8=38B5 4 %. # 27@>A;KE 1>;L=KE <5=8=38B>< ?>A;5 22545=8O 4>7K 50 <3/3
<0AAK B5;0 G5@57 2-24 G0A0 4>AB830NB AO B0:85 :=F5=B@0F88 F5DB@80:A>=0 2
F5@51@>A?8=0;L=>9 684:>AB8, :>B>@K5 2> <=>3> @07 ?@52KH0NB <8=8<0;L=K5 8=3818@CNI85
:=F5=B@0F88 4;O A0AB@0=5==KE 2>71C48B5;59 <5=8=38B0.
&5DB@80:A>= ?@>E>48B G5@57 ?;0F5=B0@=K9 10@L5@ 8 2 <0;KE :=F5=B@0F88OE 2K45;O5BAO 2
3@C4=>5 <>;>.

5B01>;87<. &5DB@80:A>= =5 ?>425@305BAO A8AB5<=>

K2545=85. 1I89 ;;8@5=A F5DB@80:A>=0 A>AB02;O5B 10-22 <;/<8=. >G5G=K9 ;;8@5=A @025=
5-12 <;/<8=. 50-60 % F5DB@80:A>=0 2K2>48BAO 2 =587<5=5==>< 2845 ?>G:0<8 8 40-50 % 2 =587
<5=5==>< 2845 A 65;GLN. 5@8>4 ?>;C2K2545=8O F5DB@80:A>=0 C 27@>A;KE A>AB02;O5B >:>;>
8 G0A>2.

\$0@<0>:8=5B8:0 2 >A>IKE ;;8=8G5A:8E A;CG0OE. # =>2>@>645==KE 45B59 ?>G:0<8 2K2>48BAO
>:>;> 70 % 4>7K. # 45B59 ?5@2KE 8 4=59 687=8, 0 B0:65 C ?0F85=B>2 AB0@H5 75 ;5B ?5@8>4
?>;C2K2545=8O 2 A@54=5< 2 2-3 @070 1>;LH5, G5< C 27@>A;KE <>;>4>3> 2>7@0AB0.
1>;L=KE A ?>G5G=>9 8;8 ?5G5=>G=>9 =54>AB0B>G=>ABLN D0@<0>:8=5B8:0 F5DB@80:A>=0 87
<5=O5BAO =57=0G8B5;L=>, >B<5G05BAO ;8HL =57=0G8B5;L=>5 C25;8G5=85 ?5@8>40
?>;C2K2545=8O. A;8 =0@CH5=0 B>;L:> DC=:F8O ?>G5.; ?>2KH05BAO 2K2545=85 A 65;GLN, 5A;8
=0@CH5=0 DC=:F8O ?5G5=8, C25;8G8205BAO 2K2545=85 ?>G:0<8.

\$0@<0F52B8G5A:85 E0@0:B5@8AB8:8.

A=>2=K5 D878:>-E8<8G5A:85 A2>9AB20: :@8AB0;;8G5A:89 ?>@>H>: ?>GB8 15;>3> 8;8 15;>3> A
65;B>20BK< >BB5=:>< F25B0, A;01> 383@>A:>?8G=K9.

5A>2<5AB8<>ABL.

&5DB@80:A>=-0@=8F0 =5;L7O A<5H820BL A :0;LF89A>45@60I8E @0AB2>@0<8, B0:8<8 :0: @0AB2>@
8=35@0 8;8 @0AB2>@ 0@B<0=0.

&5DB@80:A>= =5A>2<5AB8< A 0<, 20=:><8F8=><, D;C:>=07>;> 8 0<8=>3;8:>7840<8.

5 A;54C5B A<5H820BL A 4@C38<8 @0AB2>@8B5;O<8, :@><5 ?5@5G8A;5==KE 2 @0745;5 <!>A>1 ?@8
<5=5=8O 8 4>7K>.

!@>: 3>4=>AB8. 3 3>40.

#A;>28O E@0=5=8O. %@0=8BL 2 >@838=0;L=>9 C?0:>2:5 2 =54>ABC?=>< 4;O 45B59 <5AB5 ?@8 B5
25 °!.

#?0:>2:0.

> 0,5 3 8;8 1 3 ?>@>H:0 2> D;0:>=5; ?> 1, 5 8;8 40 D;0:>=>2 2 C?0:>2:5. > 1 D;0:>=C ?> 0,5 3 ?>@>H:0 8 1 0
@8B5;O (>40 4;O 8=J5:F89-0@=8F0 2 0 ?> 5 <;) 2 C?0:>2:5. >
1 D;0:>=C ?> 1 3 ?>@>H:0 8 1 0 @0AB2>@8B5;O (>40 4;O 8=J5:F89-0@=8F0 2 0 ?>
10 <;) 2 C?0:>2:5.

0B53>@8O >B?CA:0. > @5F5?BC.

@>872>48B5;L.

'«\$0@<0F52B8G5A:0O D8@<0 «0@=8F0».

5AB>=0E>645=85.

#: @08=0, 02093, 3. 852, C; .>@8A?>;LA:0O, 13.